MEDICAL LIBRARY

Annual Meeting Stevens Hotel, Chicago, June 18 and 19, 1948

NOV 19 1947

VOL. 34 NOVEMBER, 1947 No. 5

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

THOMAS M. McMILLAN . . Editor-in-Chief

Associate Editors

WALLACE M. YATER
SAMUEL BELLET
LOUIS B. LAPLACE

EDITORIAL BOARD

EDGAR V. ALLEN
ALFRED BLALOCK
CLARENCE E. DE LA CHAPELLE
HARRY GOLDBLATT
TINSLEY R. HARRISON
T. DUCKETT JONES
LOUIS N. KATZ
EUGENE M. LANDIS
JOHN K. LEWIS
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
HELEN B. TAUSSIG
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

Published Monthly Under the Editorial Direction of The American Heart Association

Published and Copyrighted 1946 by The C. V. Mosby Company, St. Louis, U. S. A.

Contents on Inside Cover

American Heart Journal

CONTENTS FOR NOVEMBER, 1947

Original Communications

High T Waves in the Earliest Stage of Myocardial Infarction. William Dressler, M.D., New York, N. Y., and Hugo Roesler, M.D., Philadelphia, Pa. 627

Electrolyte Changes and the Electrocardiogram in Diabetic Acidosis. Helen Eastman Martin, M.D., and Maxine Wertman, A.B., Los Angeles, Calif. 646

Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients With Congestive Heart Failure. Robert C. Batterman, M.D., and Arthur C. DeGraff, M.D., New York, N. Y. 663

Electrocardiographic Changes in Early Syphilis. Howard P. Steiger, M.D., Charlotte, N. C., and Joseph Edeiken, M.D., Philadelphia, Pa. 674

Comparative Study of Potassium Thiocyanate and Other Drugs in the Treatment of Essential Hypertension. Arthur Ruskin, M.D., and W. Frank McKinley, M.D., Galveston, Texas 691

An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. IV. The Effect of Position Change on the Relationships of the Q-T and the T-P Intervals Respectively to the Cycle Length (R-R Interval). Isadore Schlamowitz, M.D., New York, N. Y. 702

Heart Disease in the South. II. A Statistical Survey of One Hundred Seventeen Deaths Due to Rheumatic Heart Disease. Joe E. Holoubek, M.D., and Alice Baker Holoubek, M.D., Shreveport, La. 709

Heart Disease in the South. III. An Analysis of Two Hundred Seventeen Deaths Due to Arteriosclerotic Heart Disease. Joe E. Holoubek, M.D., and Alice Baker Holoubek, M.D., Shreveport, La. 715

Clinical Reports

Paroxysmal Auricular Tachycardia of Unusual Type. Benjamin R. Gendel, M.D., Memphis, Tenn. 722

Spontaneous Interstitial Emphysema of the Lung Simulating Organic Heart Disease. Edward S. McCabe, M.D., Baltimore, Md. 729

Reactions to Decholin in Circulation Time Determination. James K. Norman, M.D., Fort Worth, Texas 740

Bacillus Coli Endocarditis. D. E. Fletcher, Ph.D., Little Rock, Ark. 743

Endocardial Pockets of Left Atrium. H. K. Hellerstein, M.D., Cleveland, Ohio 751

Abstracts and Reviews

Selected Abstracts 758

Book Reviews

Book Reviews 779

American Heart Association 783

Vol. 34, No. 5, November, 1947, American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, its Possessions, Pan-American Countries, $10.00; In Canada and other Foreign countries, $11.50. Printed in the U. S. A.

American Heart Journal

VOL. 34 NOVEMBER, 1947 NO. 5

Original Communications

HIGH T WAVES IN THE EARLIEST STAGE OF MYOCARDIAL INFARCTION

WILLIAM DRESSLER, M.D., NEW YORK, N. Y., AND
HUGO ROESLER, M.D., PHILADELPHIA, PA.

HIGH T waves are known to occur in the limb and chest leads in the healing stage of myocardial infarction.[1-4] The early investigators of the electrocardiographic changes in myocardial infarction mentioned also the development of high T waves immediately following coronary occlusion. Smith[5] noted, immediately after ligation of a coronary branch in the experimental animal, an increase of the amplitude of the T wave proportionate to the size of the ligated artery. When a large artery was occluded, the T wave became tall and exceeded the height of the R deflection. Within twenty-four hours the large T wave became sharply inverted. Pardee,[6] in his first report on the electrocardiogram in myocardial infarction, stated that records taken shortly after obstruction of a coronary branch may have as typical features "the extreme height of the T wave and the fact that this wave starts from a point of the QRS group well away from the base line." Later investigators[4,7-10] failed to describe high T waves as an early feature in myocardial infarction, possibly because they were more impressed with the elevation of S-T, or perhaps because the overwhelming number of clinical investigations dealt primarily with subacute stages of infarction. Nor are high T waves as an early sign of infarction mentioned by the majority of current cardiologic textbooks.[11-14] Bohning and Katz[3] have reported "transient elevation of the T wave" in a few cases in which the clinical picture was suspicious of coronary occlusion.

We have observed cases in which high T waves were the outstanding feature in the earliest stage of myocardial infarction, when elevation of S-T and signifi-

From the Department of Medicine, Israel Zion Division, Maimonides Hospital, Brooklyn, N. Y., and the Departments of Medicine and Radiology, Temple University Hospital and Medical School, Philadelphia, Pa.

Received for publication Feb. 18, 1947.

cant changes of QRS were absent. Such observations prompted our study, which is the subject of this report. It includes twenty-seven instances of recent myocardial infarction which were observed in twenty-four patients. In all cases early electrocardiograms were taken, some as early as one and one-quarter hours and none later than twelve hours after the beginning of the attack. In all but two cases follow-up tracings were obtained. In thirteen instances serial records were made daily or at intervals of several hours.

CASE REPORTS

CASE 1.—J. B. was a 58-year-old man. While working on May 8, 1944, he experienced severe pain in the left side of the chest and in the left arm and almost fainted. The pain lasted for several hours and was not quite relieved by morphine. The attack was followed by low-grade fever and increase of the white blood count and sedimentation rate.

The first electrocardiogram (Fig. 1, *A*) was taken three and one-half hours after the onset of symptoms. In Lead I the amplitude of the upright T is 3.5 mm.; there is no elevation of the S-T junction. Lead CF_4 (the only chest lead taken at the first examination) shows a small Q, a rather high R deflection, and a conspicuous S wave. The S-T junction is 2.2 mm. above the base line; the amplitude of the T deflection is 20 millimeters.

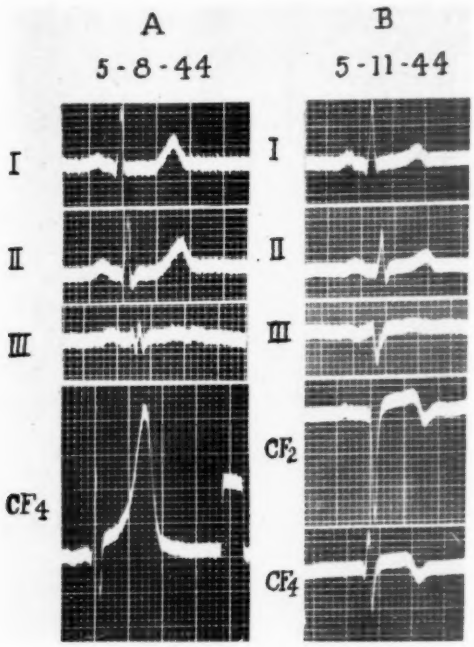


Fig. 1.—Case 1. Signs diagnostic of anteroseptal infarction. Tracing *A*, taken three and one-half hours after the onset of symptoms, shows high T waves in Leads I and CF_4, without abnormal elevation of S-T or significant changes of QRS. *B*, Three days after the coronary attack. The chest leads show significant charges of QRS and inversion of T.

The second electrocardiogram (Fig. 1, *B*) was taken three days after the attack. It shows marked decrease of the amplitude of the T waves. A deep QS deflection is present in Lead CF_2. The amplitude of R has decreased in Lead CR_4. In both chest leads the T wave is mainly inverted.

Summary.—An electrocardiogram taken three days after a coronary attack was diagnostic of anteroseptal infarction. In the first electrocardiogram, which was obtained three and one-half hours after the onset of symptoms, high T waves in the limb leads and especially in the chest lead were the outstanding diagnostic feature. In this early stage significant changes of QRS and abnormal elevation of S-T were absent.

CASE 2.—H. L., a 50-year-old man, had suffered from hypertension for many years. On Sept. 22, 1939, while playing cards, he was seized with severe precordial pain which radiated to the left shoulder and arm and caused him to perspire profusely. On the next day the blood pressure was 90/70 and the white blood count was 13,800.

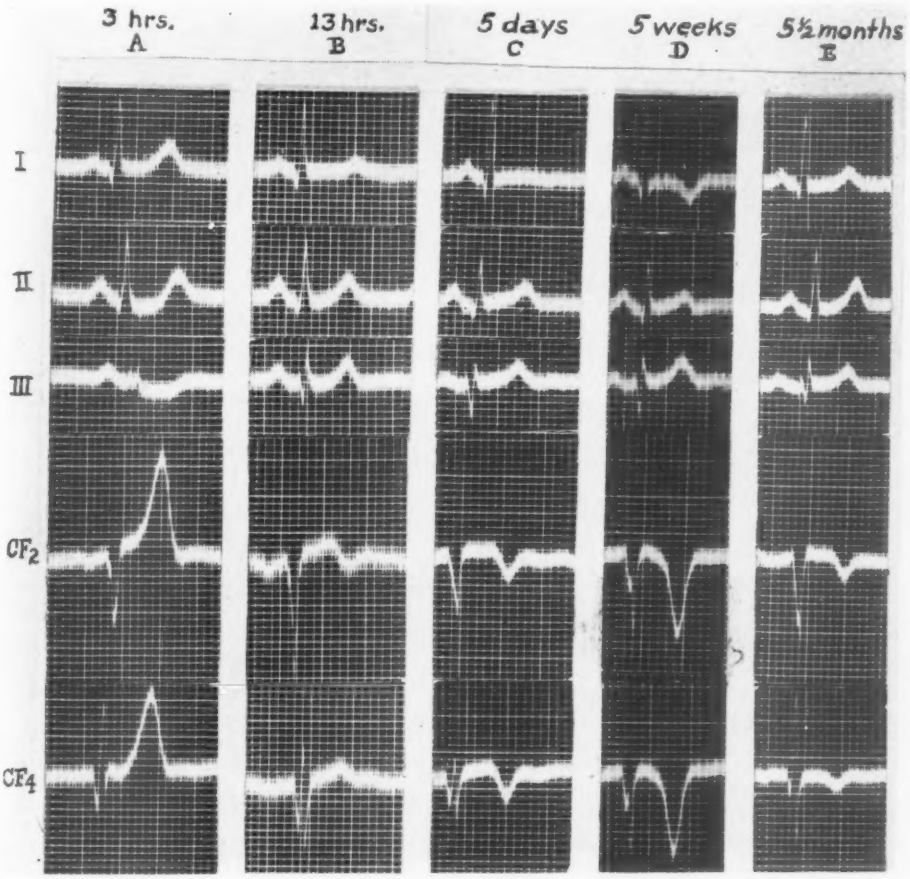


Fig. 2.—Case 2. Signs diagnostic of anteroseptal infarction. Tracing *A*, taken three hours after the onset of symptoms, shows, in addition to significant Q waves in the chest leads, high T waves in Lead I and especially in the chest leads without significant elevation of S-T. *B*, *C*, and *D* show inversion of the high T waves. *E* shows regressive changes.

The first electrocardiogram (Fig. 2, *A*) was taken three hours after the onset of symptoms. It shows marked depression of S-T in Leads II and III, but no significant elevation of S-T in Lead I. The amplitude of T_1 is 3 millimeters. Lead CF_2 shows a deep QS deflection and Lead CF_4,

a significant Q wave. In both chest leads the T waves are usually high; their amplitude is 14 mm. in Lead CF_2 and 12 mm. in Lead CF_4. The high T waves are not associated with significant elevation of S-T.

The second electrocardiogram (Fig. 2, *B*), which was taken thirteen hours after the onset of symptoms, shows marked decrease in the amplitude of T in Lead I and in the chest leads. In Lead CF_2 the T wave is semi-inverted. The next two tracings (*C* and *D*) which were taken five days and five weeks, respectively, after the onset of symptoms, show complete inversion of T in Lead I and in the chest leads. In tracing *E*, which was obtained five and one-half months after the attack, regressive changes of T are noted.

Summary.—The electrocardiograms were diagnostic of anteroseptal infarction. In the early stage of infarction, three hours after the onset of symptoms, high T waves were noted in Lead I and especially in the chest leads; they were no longer present thirteen hours after the beginning of the attack. The high T waves were not associated with abnormal elevation of S-T.

CASE 4.—L. C., was a 36-year-old man. In the latter part of November, 1945, he suddenly felt as though he had been "hit in the epigastric notch." Three weeks later, while working, he had what he considered to be indigestion; again there was distress in the epigastric region. Similar attacks occurred more often during the first two weeks of March and were not related to intake of food. They lasted from ten to fifteen minutes. At 2 P.M. on March 14, 1946, the patient experienced a burning sensation in the epigastrium and perspired profusely. He vomited and felt weak. When he was brought to the accident dispensary, he still complained of a pressing and burning sensation behind the sternum. The blood pressure was 90/70. The white blood count was 17,100. The sedimentation rate was normal. On the next day the temperature rose and remained above normal for nine days. The sedimentation rate was elevated on the fourth day after the attack.

The first electrocardiogram (Fig. 3, *A*) was taken three hours after the onset of symptoms. It shows high T waves in Lead I and especially in the chest leads. Instead of elevation, marked depression and upward concavity of S-T is noted, notably in Leads CR_3 through CR_6. No significant changes in QRS are present.

Fig. 3, *B*, was taken eighteen hours after the onset of symptoms. It shows marked decrease of the amplitude of R and T in all leads except Leads II and III. A significant Q wave is present in Leads I and CR_1. The R deflection is very small in Leads CR_1 through CR_3. Elevation of S-T is noted where depression was previously present. The T wave is semi-inverted in Leads I and CR_2 through CR_4.

Three days after the attack (Fig. 3, *C*) inversion of T is noted in all leads except Leads II, III, and CF_1. A week after the attack (Fig. 3, *D*) inversion of T is more pronounced while elevation of S-T is regressive.

Summary.—The electrocardiograms were diagnostic of anteroseptal infarction. In the earliest stage, three hours after the onset of symptoms, unusual electrocardiographic changes were observed: marked depression of S-T associated with abnormally high T waves in Lead I and in the chest leads. Significant changes of QRS did not appear until eighteen hours after the onset of symptoms, when depression of S-T was replaced by elevation, and the high T waves were decreased in amplitude and became semi-inverted.

CASE 15.—M. N. was a 42-year-old man. On June 16, 1944, while convalescing from pleuropneumonia, he was suddenly seized with severe pressing pain across his chest which radiated to the left arm. He was nauseated and vomited. The attack was followed by a rise in temperature and increase of the sedimentation rate.

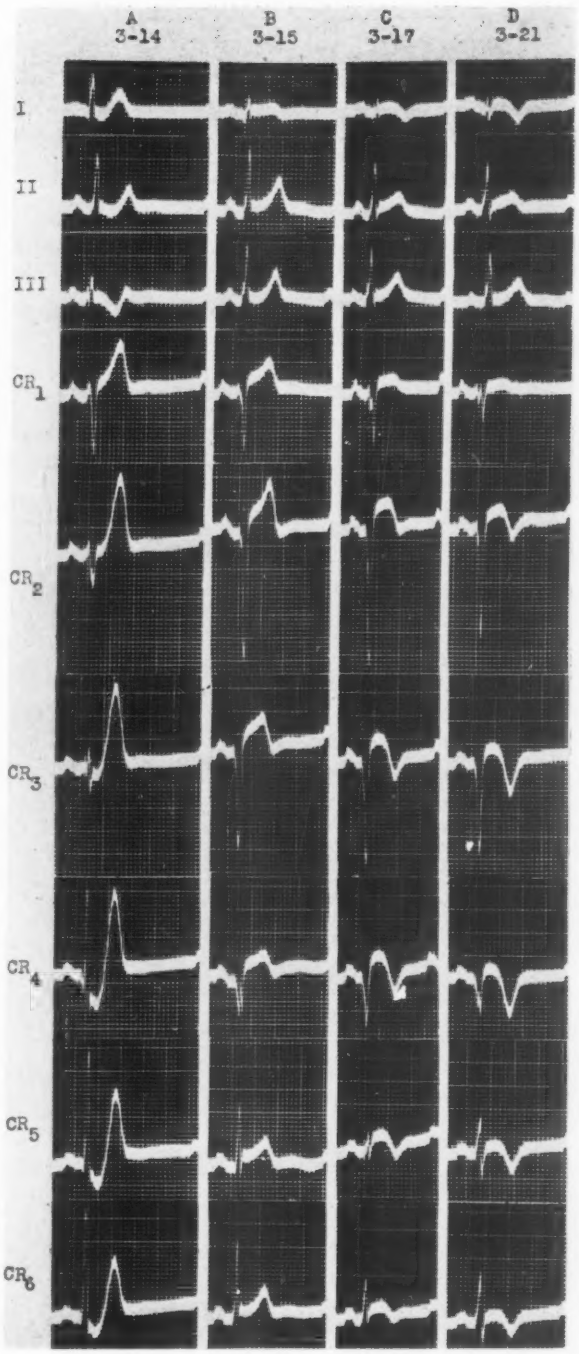


Fig. 3.—Case 4. Signs diagnostic of anteroseptal infarction. Tracing *A*, obtained three hours after the onset of the attack, shows high T waves in Lead I and in the chest leads associated with abnormal depression of S-T; this is especially distinct in Leads CR_3 through CR_6. Significant changes in QRS were not present until eighteen hours after the onset of symptoms (tracing *B*), when the high T waves had decreased in amplitude and become semi-inverted. *C* and *D*, Progressive inversion of the previously high T waves.

The first electrocardiogram (Fig. 4, *A*) was taken on the day of the attack. It shows an insignificant Q wave in Leads I and II, and an S deflection in Lead III. The S-T junction is depressed in Lead I and slightly elevated in Lead III. T_1 is inverted and T_3 is upright; its amplitude is 4.3 millimeters. The chest leads are normal except that the T wave in Lead CF_4 is of low voltage and notched.

A second tracing (Fig. 4, *B*) was taken three days after the attack. It shows in Leads II and III changes of QRS and T that are characteristic of posterior infarction. The amplitude of T_2 is diminished; T_3 has become inverted. In the chest leads the amplitude of the T waves has increased.

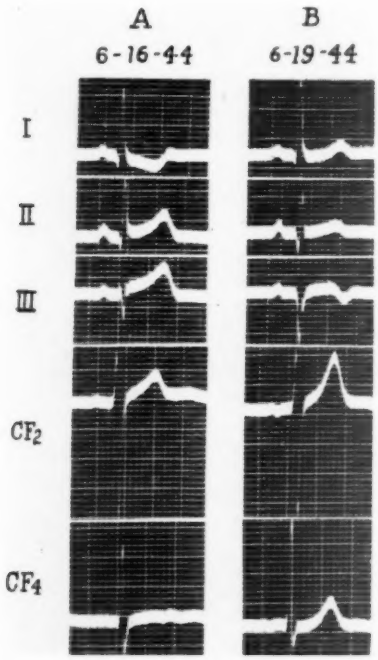


Fig. 4.—Case 15. Signs diagnostic of posterior infarction. Tracing *A*, obtained on the day of the attack, shows high T waves in Lead III without abnormal elevation of S-T or siginficant changes of QRS. *B*, Three days after the coronary attack. Deep Q waves in Leads II and III and inversion of T_3.

Summary.—The electrocardiograms were diagnostic of posterior wall infarction. The first tracing, which was obtained on the day of the attack, showed unusually high T waves in Lead III without significant elevation of S-T or changes in QRS. Transient change of T in Lead CF_4 was probably due temporary involvement of the lateral wall.

CASE 16.—J. M. was a 70-year-old man. On March 11, 1946, while walking to the hospital to receive treatment for intermittent claudication, he was seized with severe pain in the region of the lower portion of the sternum and in the epigastrium. The pain continued for more than an hour after the patient arrived in the hospital; morphine was then given. The white blood count was 15,200. One day after the attack the temperature rose and remained above normal for three days. The sedimentation rate was increased.

The first electrocardiogram (Fig. 5, *A*) was obtained two and one-half hours after the onset of symptoms. It shows a high T wave in Lead III; its amplitude is 3 millimeters. The S-T junction is only slightly above the base line in Leads II and III. There is marked depression of S-T and inversion of T in Lead I and in the chest leads. Significant changes of QRS are absent.

Fig. 5, *B*, was taken three days after the attack. It shows in Leads II and III changes of QRS and T that are characteristic of posterior wall infarction. T_2 and T_3 have become inverted, while in the chest leads the T waves have become upright. There is still slight depression of S-T in the chest leads. In the next tracing (Fig. 5, *C*), taken nine days after the attack, depression of S-T has disappeared.

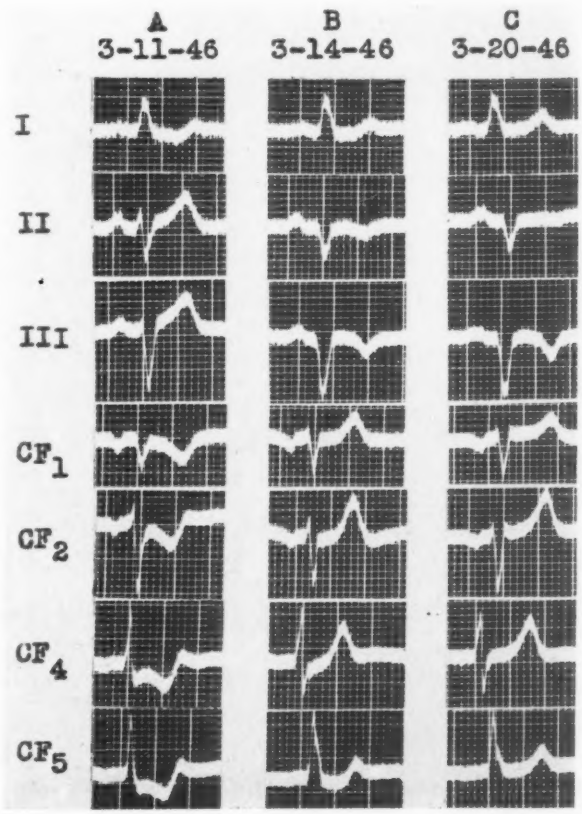


Fig. 5.—Case 16. Signs disgnostic of posterior infarction. Tracing *A*, obtained two and one-half hours after the onset of the attack, shows, in addition to depression of S-T and inversion of T in Lead I and in the chest leads, high T waves in Leads II and III. The latter are not associated with abnormal elevation of S-T nor with significant changes of QRS. *B* and *C*. Deep Q waves and inverted T waves in Leads II and III. Upright T waves in the chest leads.

Summary.—The electrocardiograms were diagnostic of posterior wall infarction. The first tracing, which was obtained two and one-half hours after the onset of symptoms, showed a high T wave in Lead III without significant elevation of S-T or changes in QRS. There were, however, distinct depression of S-T and inversion of T in Lead I and in the chest leads.

CASE 17.—J. T., a 47-year-old man, had suffered from exertional dyspnea for the last five years. While resting on the evening of July 31, 1945, he experienced substernal pain of five minutes' duration. On Aug. 1, 1945, he again felt substernal pain which was accompanied by belching and profuse perspiration. On this occasion the distress lasted for three hours, until relieved by morphine. Then low-grade fever developed and the sedimentation rate was increased.

The first electrocardiogram (Fig. 6, *A*) was taken two and one-half hours after the onset of symptoms. It shows in Leads II and III high T waves without significant evelation of S-T or changes in QRS. The amplitude of T_3 is 3 millimeters. In the chest leads there is slight depression of S-T.

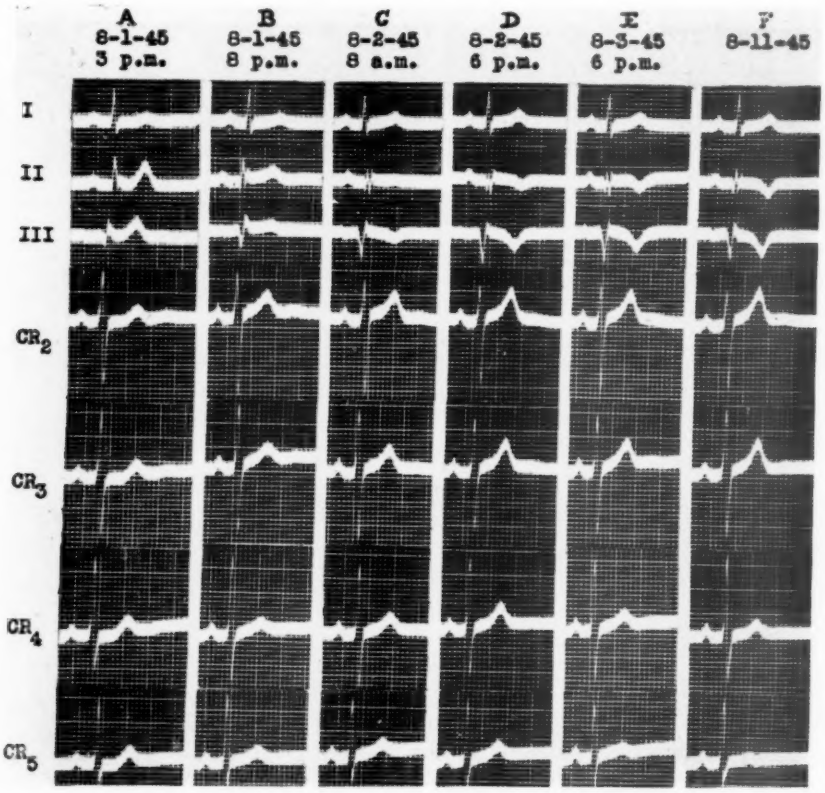


Fig. 6.—Case 17. Signs diagnostic of posterior infarction. Tracing *A*, obtained two and one-half hours after the onset of symptoms, shows, in addition to slight depression of S-T in Lead I and in the chest leads, high T waves in Leads II and III. The latter are not associated with abnormal elevation of S-T. Significant changes of QRS in Leads II and III did not appear until nineteen hours after the beginning of the attack (tracing *C*); they developed simultaneously with inversion of T_3. *D*, *E*, and *F*, Progressive inversion of T_2 and T_3.

Fig. 6, *B*, was taken seven hours after the attack. A small Q wave has developed in Lead II, and Q_3 has deepened. The voltage of T_2 and T_3 has markedly decreased.

Fig. 6, *C*, was taken nineteen hours after the beginning of the attack. Q_3 has broadened and deepened. T_3 has become inverted. In the following tracing (Fig. 6, *D*), which was obtained twenty-nine hours after the onset of symptoms, significant changes in QRS and inversion of T are noted in Leads II and III. The amplitude of T has increased in Leads CR_2 through CR_4. *E* and *F* of Fig. 6 were taken two days and ten days, respectively, after the attack. Inversion of T_2 and T_3 is even more pronounced. In Lead CR_5 the T wave has become low and diphasic.

Summary.—The electrocardiograms were diagnostic of posterior wall infarction, probably extending to the lateral wall. In the earliest stage, two and one-half hours after the onset of symptoms, the outstanding electrocardiographic feature was high T waves in Leads II and III, not accompanied by abnormal elevation of S-T nor by significant changes of QRS. Slight depression of S-T was noted in the chest leads. It was not until nineteen hours after the beginning of the attack that significant Q waves appeared in Leads II and III, after T_3 had already become inverted.

CASE 23.—F. N. was a 59-year-old man. At 2 P.M. on Sept. 4, 1944, he experienced severe pain across his chest and in both arms. He looked pale and perspired. Morphine was required to relieve the pain. The blood pressure on that day was 190/120. On the following day the white blood count was 16,400 and the sedimentation rate was increased. On Sept. 6, 1944, there was another attack of similar pain which lasted all day long.

The first electrocardiogram (Fig. 7, *A*) was taken one and one-half hours after the beginning of the first attack of pain. In Leads II and III it shows small Q deflections, marked elevation of S-T, and unusually high T waves. In the chest leads there is marked depression of S-T.

Fig. 7, *B*, was taken one day after *A*. In Leads II and III there are significant Q waves and inverted T waves. In the chest leads, the S-T segment is only slightly depressed and the T waves have reached remarkable height, especially in Leads CR_2 and CR_4. In Fig. 7, *C*, which was obtained two days after *A*, the leads from the right side of the chest show further increase in the amplitude of T. On the other hand, in Lead CR_5 the S-T segment is somewhat elevated and runs a straight course.

Fig. 7, *D*, was obtained one day after the second attack of severe chest pain. It shows marked changes in Leads CR_3 through CR_5; the S-T segment is abnormally elevated and the amplitude of the T waves has further increased, while significant changes of QRS are absent. Tracings *E* through *H*, taken daily, show in Leads CR_3 through CR_5 a gradual return of the S-T segment to the base line accompanied by a decrease in the amplitude of T. In the last two tracings (*I* and *J*) significant changes of QRS and inversion of T are noted in the leads from the left side of the chest and in Lead I, indicating lateral wall infarction.

Summary.—There were two attacks of prolonged chest distress which occurred at an interval of two days. After the first attack the electrocardiogram was diagnostic of posterior infarction. In the earliest stage, one and one-half hours after the onset of symptoms, high T waves were seen in Leads II and III, associated with marked elevation of S-T. Later, in the healing stage of the posterior infarction, high T waves appeared in the chest leads. The second attack was followed by changes in the electrocardiogram which pointed to lateral infarction. The earliest stage was marked by further increase in the amplitude of the high T waves which had developed in the chest leads during the healing stage of the posterior infarction; there was also marked elevation of S-T. Six days passed before significant changes of QRS developed in the chest leads. During this period the high T waves gradually decreased in amplitude and became finally inverted.

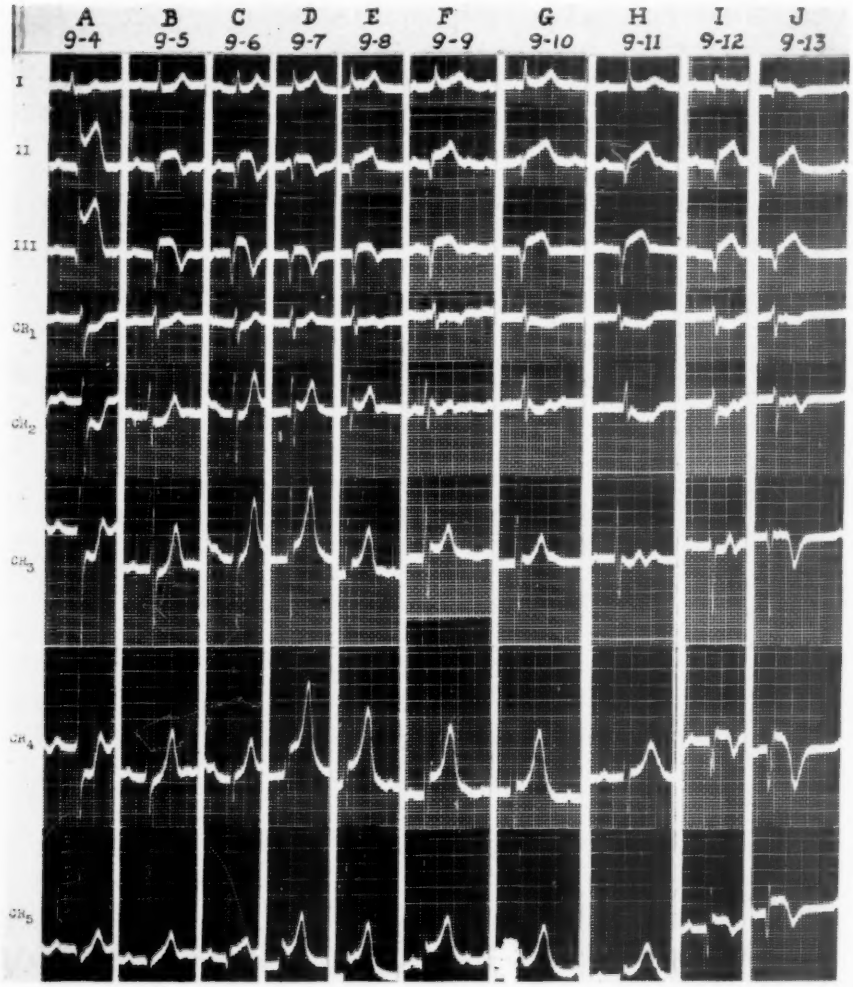


Fig. 7.—Case 23. Prolonged attacks of severe precordial distress occurred on September 4 and 6. After the first attack, signs of posterior wall infarction developed (tracings *A* and *B*). Tracing *A*, obtained one and one-half hours after the beginning of the first attack, shows in Leads II and III marked elevation of S-T and unusually high T waves. Significant changes of QRS in Leads II and III did not appear until a day after the attack (tracing *B*) and were simultaneous with inversion of T_2 and T_3 and with increase of the amplitude of T in the chest leads. Tracing *D* was obtained after the second attack of prolonged chest distress. It shows further increase of the T waves and elevation of S-T in Leads I and CR_1 through CR_5. Significant changes of QRS in these leads developed only six days after the attack (tracings *I* and *J*), when the T waves had become inverted. These changes pointed to lateral wall infarction.

COMMENT

The presence of myocardial infarction in the cases presented in this report (Table I) was proved by post-mortem examination in four instances, and in the remainder, by clinical, electrocardiographic, and other laboratory evidence. Anterior wall infarction was observed sixteen times and infarction of the pos-

terior wall, eleven times. In three cases, anterior and posterior infarctions occurred either simultaneously or in short sequence.

In all but two instances of infarction high T waves were observed during the earliest stage of infarction. They were seen in those leads in which inversion of T developed during the healing stage. In one of the cases where high T waves were absent (Case 6), the first electrocardiogram, taken on the day of the attack, already showed signs of healing (anterior) infarction, that is, inversion of T_1 and high T waves in Lead III.

The term "high T wave," as used in this report, needs amplification. In eight cases the amplitude of the significant T waves exceeded the maximum normal range; in six instances of posterior wall infarction the amplitude of T_3 was more than 3.4 mm.,[15] in two cases of anterior wall infarction the T waves in the chest leads were of unusual amplitude.[16] In no instance of anterior wall infarction were T waves in Lead I observed which had an amplitude above the maximum normal.

In thirteen instances the amplitude of the significant T waves was conspicuously in excess of the normal mean values which have been reported by various investigators.[13,17]

In four of our cases electrocardiograms which had been obtained prior to the attack were available for comparison. Tracings taken shortly after the attack showed marked increase in the height of those T waves which later underwent inversion.

In thirteen instances where serial tracings were available (taken after the attack at intervals of several hours, or daily) it was possible to determine how long the high T waves persisted. In eight cases they were no longer present one day after the attack. In one of these cases (Case 21) high T waves still could be observed eight hours after the onset of symptoms but had disappeared five hours later. In Case 8 the high T waves, which were observed shortly after the beginning of the attack, were no longer present seven hours after the onset of symptoms.

Persistence of the high T waves for more than twenty-four hours was observed in five cases. In one case (Case 14) they were present for two weeks until death. Early death, that is, within several days after the attack, occurred in 60 per cent of the patients with persistent high T waves, but in only 14 per cent of the cases in which the high T waves disappeared within twenty-four hours. Persistent high T waves, as a rule, were associated with persistent elevation of the S-T junction.

High T waves in cases of myocardial infarction are possibly due to the release of potassium from the interior of injured muscle cells.[13] They are part of the injury pattern[22] like upward displacement of the S-T junction. In the cases of our study, high T waves were usually associated with abnormal elevation of S-T. However, in three cases of posterior wall infarction which showed high T waves in Lead III, and in three cases of anterior wall infarction in which high T waves were observed in the chest leads, abnormal elevation of S-T was absent. In five of these cases the S-T junction was either at the isoelectric level or was elevated within normal range. A sixth case (Case 4) which presented the

TABLE I. CHANGES IN EARLY AND FOLLOW-UP ELECTROCARDIOGRAMS IN TWENTY-SEVEN INSTANCES OF MYOCARDIAL INFARCTION (TWENTY-FOUR CASES)

CASE	NAME	AGE	FIRST ELECTROCARDIOGRAM					FOLLOW-UP ELECTROCARDIOGRAM	DIAGNOSIS		REMARKS
			AFTER ONSET OF SYMPTOMS	HIGH T WAVES	S-T SEGMENT	R WAVES	SIGNIFICANT Q		CLINICAL AND ELECTROCARDIOGRAPHIC	AUTOPSY	
1	J. B.	58	3½ hours	In Lead I; huge T in CF_4	Elevated 2.2 mm. in CF_4	Normal	—	Three days later, R deflection absent in CF_2, its amplitude greatly diminished in CF_4. T_1 much lower; inversion of T in CF_2 and CF_4	Anteroseptal infarction		
2	H. L.	50	3 hours	In Leads I, CF_2, and CF_4	No abnormal elevation	Absent in CF_2	In CF_4	After 13 hours, amplitude of T much diminished in Leads I, CF_2, and CF_4. T semi-inverted in CF_2. After 5 days, T inverted in CF_2 and CF_4, flat in Lead I	Anteroseptal infarction		
3	C. W.	51	Day of attack	In Leads CF_2, CF_4, and CF_5	Abnormally elevated in Leads CF_2, CF_4, and CF_5	Within normal limits	In CF_2	One day later, the R wave has disappeared in CF_2 and CF_4; T lower in Lead I, lower and diphasic in CF_2, CF_4, and CF_5	Anteroseptal infarction		
4	L. C.	36	3 hours	In Leads I, CR_1-CR_6	Abnormally depressed in Leads I, CR_3-CR_6	Within normal limits	—	18 hours after onset of symptoms, abnormal Q in Lead I; R tiny in CR_1-CR_3, absent in CR_4. S-T elevated in leads where it was previously depressed. T of diminished voltage in Leads I, CR_1-CR_6, diphasic in Leads I, CR_2-CR_4. After 3 days, inversion of T in Leads I, CR_3-CR_6	Anteroseptal infarction		The case shows the transition from the stage of subendocardial injury to infarction involving the subepicardial muscle layers

5	H. B.	35	3 hours	In Leads I, CR_2-CR_5	Abnormally elevated in CR_2-CR_4	Within normal limits	—	10 weeks later, R absent in CR_2, of diminished voltage in CR_3-CR_5; S-T not abnormally elevated; T of diminished voltage where it was previously high. Diphasic T in CR_3	Anteroseptal infarction		
6	B. L.	56	Day of attack	In Lead III	Elevated 3 mm. in CF_3, depressed in Leads I and CF_4	Rudimentary in CF_2	—	3 weeks later, R of diminished amplitude in CF_3 and CF_4; no significant deviation of S-T; T sharply inverted in Leads I, CF_2, CF_3, and CF_4, abnormally high in Lead III. Death 2½ years after the attack	Anteroseptal infarction	Infarction scar in anterior wall of left ventricle close to interventricular septum	First electrocardiogram already showed changes usually observed in healing stage of anterior infarction
7	C. C.	55	2 hours	Increase in amplitude of T in CR_2, CR_3, and CR_4	Abnormally elevated in CR_2 and CR_3	Of diminished amplitude in CR_2 and CR_3	—	1 day later, deep Q in CR_2; R of diminished voltage in CR_3. The voltage of T diminished in CR_2, CR_3, and CR_4. 4 days later, R rudimentary in CR_2, absent in CR_3. 10 days later, T_1 flat, inversion of T in CR_2, CR_3, and CR_4	Anteroseptal infarction		An electrocardiogram taken 2 days prior to the attack was available for comparison
8	H. W.	52	3½ hours	In CF_1, CF_3, and CF_4	Abnormally elevated in Leads I, CF_1, CF_3, and CF_4	Within normal limits	Small Q in CF_3	7 hours after onset of symptoms, R absent in CF_3; amplitude of T diminished in CF_1, CF_3, and CF_4; beginning inversion of T in all chest leads. 12 hours after onset of symptoms, R rudimentary in CF_4, T inverted in Lead I and all chest leads	Anteroseptal infarction		
9	E. D.	45	1¼ hours	In Leads I, and CR_2-CR_6	Abnormally elevated in Leads I and CR_2-CR_5	Rudimentary in CR_2, absent in CR_3 and CR_4	In Leads I and CR_2	1 day later, the T wave in Leads I, CR_5, and CR_6 shows diminished voltage and is diphasic. The elevated S-T segments and high T waves in Leads CR_1-CR_4 show almost no regressive changes until death 6 days after the attack	Extensive anterior infarction		

TABLE I. CHANGES IN EARLY AND FOLLOW-UP ELECTROCARDIOGRAMS IN TWENTY-SEVEN INSTANCES OF MYOCARDIAL INFARCTION (TWENTY-FOUR CASES)—CONT'D

CASE	NAME	AGE	FIRST ELECTROCARDIOGRAM					FOLLOW-UP ELECTROCARDIOGRAM	DIAGNOSIS		REMARKS
			AFTER ONSET OF SYMPTOMS	HIGH T WAVES	S-T SEGMENT	R WAVES	SIGNIFICANT Q		CLINICAL AND ELECTROCARDIOGRAPHIC	AUTOPSY	
10	P. T.	39	Day of attack	In Leads I, CF_2, and CF_4	Abnormally elevated in CF_2 and CF_4	Within normal limits	—	Very slow decrease in voltage of T in Leads I, CF_2, and CF_4. Semi-inversion of T in these leads is noted only 11 days after the attack. No significant changes of QRS developed	Anteroseptal infarction		
11	C. G.	63	5 hours	In CF_2 and CF_4	Abnormally elevated in CF_2 and CF_4	Absent in CF_2 and CF_4	—	1 day after the attack, T waves in CF_2 and CF_4 show diminished voltage and terminal inversion. Death 3 days after the attack	Anteroseptal infarction	Recent anteroseptal infarction	
12	N. T.	41	$5^3/_4$ hours	In CF_3 and CF_4	Abnormally elevated in CF_3-CF_5	Tiny in CF_3, absent in CF_4	—		Anterior infarction		
13	N. E.	44	7 hours	In CF_2 and CF_3	Abnormally elevated in CF_2 and CF_3	Normal in CF_2 and CF_3, of low voltage in limb leads	In Leads II and III	3 days after the attack, right bundle branch block. Progressive changes of QRS and T in Leads II and III. inversion of T in CF_2 and CF_3. Death 9 days after the attack	Acute anteroseptal and posterior infarctions	Extensive recent infarction of interventricular septum, involving its entire width and extending posteriorly over apical region of left ventricle	

14	E. P.	56	Day of attack	Increase of T in Leads III, CF_3, and CF_4	Abnormal elevation in CF_3 and CF_4	Slight decrease in amplitude of R in CF_3 and CF_4, as compared with a previous tracing	——	8 hours after first tracing on day of attack, R is invisible in CF_3 and of reduced amplitude in CF_4. Amplitude of T is somewhat diminished in Leads III, CF_3, and CF_4. A significant Q is seen in Lead III. T_2 and T_3 are diphasic. 1 day after attack, T_2 and T_3 are inverted. In the following 12 days, the elevated S-T and high T in CF_3 and CF_4 show almost no tendency to regressive changes. Death occurred 19 days after the attack	Acute anteroseptal and posterior infarctions	Recent infarction of the whole width of the interventricular septum and of the anterior and posterior aspects of left left ventricle	An electrocardiogram taken 11 months prior to the last attack was available for comparison
15	M. N.	42	Day of attack	In Leads II and III	No abnormal elevation	Tiny in Lead III	——	3 days after onset of symptoms, significant Q in Leads II and III; T_3 inverted, amplitude of T_2 greatly reduced. Increase in height of T in CF_2 and CF_4	Posterior infarction		
16	J. M.	70	2½ hours	In Leads II and III	No abnormal elevation. Abnormal depression in all chest leads	Small in Lead III	——	3 days after onset of symptoms, significant Q and inverted T in Leads II and III. In the chest leads, depression of S-T very slight and T upright again	Posterior infarction		
17	J. T.	47	2½ hours	In Leads II and III	No abnormal elevation. Slight depression in CR_2-CR_5	Low voltage in limb leads	——	7 hours after onset of symptoms, small Q in Lead II, deep Q in Lead III. Amplitude of T greatly diminished in Leads II, III, CR_4, and CR_5, increased in CR_2 and CR_3. 19 hours after onset of symptoms, Q_3 larger, T_3 inverted. 29 hours after onset of symptoms, T_2 inverted. 2 days after onset of symptoms, T in CR_5 low and diphasic	Posterolateral infarction		
18	J. N.	50	3 hours	In Leads II and III	Abnormally elevated in Leads II and III	Within normal limits	In Leads II and III	8 days after attack, inversion of T_2 and T_3. Death 10 days after attack	Posterior infarction		

TABLE I. CHANGES IN EARLY AND FOLLOW-UP ELECTROCARDIOGRAMS IN TWENTY-SEVEN INSTANCES OF MYOCARDIAL INFARCTION (TWENTY-FOUR CASES)—CONT'D

CASE	NAME	AGE	FIRST ELECTROCARDIOGRAM					FOLLOW-UP ELECTROCARDIOGRAM	DIAGNOSIS		REMARKS
			AFTER ONSET OF SYMPTOMS	HIGH T WAVES	S-T SEGMENT	R WAVES	SIGNIFICANT Q		CLINICAL AND ELECTROCARDIOGRAPHIC	AUTOPSY	
19	N. A.	69	2 hours	In CF_3	Abnormally elevated in CF_3 and CF_5	Absent in CF_3	In Leads I, CF_3, and CF_5	Death one day after attack	Anterior infarction		
20	A. P.	62	7 hours	In Leads II and III	Abnormally elevated in Leads II and III, depressed in Leads I, CR_2, and CR_4	Within normal limits	Small Q in Leads II and III	15 hours after onset of symptoms, significant Q in Leads II and III; S-T segment approaching base line and T inverted in Leads II and III. Very slight depression of S-T in CR_2 and CR_4	Posterior infarction		
21	W. D.	61	3 hours	In Leads II and III	Abnormally elevated in Leads II and III, depressed in Lead IV F	Within normal limits	Small Q in Leads II and III	8 hours after onset of symptoms, amplitude of T_3 much reduced; diminished elevation of S-T in Lead III. 13 hours after onset of symptoms: in Lead III the Q wave broader but not yet of significant size; T_3 low and M-shaped. 24 hours after onset of symptoms, no significant change. 32 hours after onset of symptoms, significant Q_3; T_2 diphasic, T_3 inverted	Posterior infarction		First appearance of significant Q_3 32 hours after onset of symptoms
22	H. W.	41	Day of attack ("right after onset")	In Leads II and III	Abnormally elevated in Leads II and III, depressed in Lead I	Within normal limits	In Leads II and III (were present prior to attack, as residual of former attack)	6 days after attack, "Coronary T waves" in Leads II and III. 8 days after attack, T waves upright again in Leads II and III	Posterior infarction		An electrocardiogram taken 1 day prior to attack was available for comparison

23	F. N.	59	1½ hours after first attack	In Leads II and III	Markedly elevated in Leads II and III; depressed in Leads I and CR_2-CR_5	Within normal limits	Small Q waves in Leads II and III	1 day after attack, significant Q waves and inverted T waves in Leads II and III. Increase in amplitude of T in CR_2-CR_5	Posterior infarction		Two attacks occurred at an interval of 2 days. An electrocardiogram taken a day prior to the second attack was available for comparison. Although it already showed high T waves in Leads I, CR_2, and CR_3 because of posterior infarction, an increase in the amplitude of these high T waves was observed after the second attack It took 6 days after the second attack until significant changes of QRS developed
			Within 24 hours of a new severe attack which occurred 2 days after first attack	In Leads I and CR_3-CR_5	Markedly elevated in CR_3-CR_5	Within normal limits	In Leads II and III (residuals of previous attack)	2 days after attack, amplitude of T reduced in CR_2-CR_4. Still marked elevation of S-T in CR_3-CR_5. 3 days after the attack, T smaller in Leads I, CR_2-CR_5. 5 days after attack, T of diminished voltage in Leads I, CR_3-CR_5. 6 days after attack, amplitude of R markedly reduced in Leads I, CR_2, CR_3, and CR_5; QS deflection in CR_4; significant Q in Leads I and CR_5; T diphasic in Leads I and CR_3, inverted in CR_4 and CR_5. 7 days after attack, T sharply inverted in Leads I, CR_2-CR_5	Anterolateral infarction		
24	J. S.	70	Day of attack	In Lead III (with terminal inversion)	Abnormally elevated in Lead III, depressed in CF_3 and CF_5	Of low amplitude in Lead III	In Lead II	9 days after attack, Q in Lead II, and downward deflection of QRS in Lead III have deepened. Elevation of S-T in Lead III has disappeared, T_2 and T_3 are inverted	Posterior infarction		Right bundle branch block

features of anterior wall infarction was unique, in our experience, inasmuch as it showed high T waves, especially in the chest leads, coupled with abnormal depression of S-T. Downward displacement of S-T in limb and chest leads is sometimes observed in patients in whom repeated anginal attacks constitute a prolonged "prodromal stage" prior to the appearance of classical signs of myocardial infarction. In such patients, depression of S-T is thought to indicate marked coronary insufficiency which has caused injury primarily to the subendocardial muscle layers.[18-21] We believe that the first tracing in Case 4 depicts a transitional stage which was the result of an extension of injury from the subendocardial to the subepicardial muscle layers, possibly due to progression from incomplete to complete coronary occlusion.

In fifteen cases high T waves appeared earlier than significant changes in the QRS complexes. The latter were either absent altogether in the early stage or (in five cases) there were some suspicious changes of QRS, such as a decrease in the size of the R deflections or small Q waves in Leads II and III. In most of these cases significant changes of QRS developed within twenty-four hours after the onset of symptoms when the high T waves were already in the regressive stage. In one case (Case 23) significant Q waves did not appear until six days after the attack. There were two instances in which significant changes of QRS failed to develop while the high T wave became gradually inverted.

In five cases high T waves in the earliest stage of myocardial infarction were associated neither with abnormal elevation of S-T nor with significant changes of QRS. These cases included three instances of posterior wall infarction (Cases 15, 16, and 17) and two instances of anterior infarction (Cases 1 and 4). Thus, in 18 per cent of our cases, high T waves represented the leading diagnostic sign in the earliest stage of myocardial infarction.

SUMMARY

Twenty-seven instances of myocardial infarction were studied, in which the first electrocardiogram was taken as early as one and one-quarter hours, and not later than twelve hours, after the onset of symptoms. Follow-up tracings were obtained in all but two of these cases. In thirteen cases serial records, taken daily or at intervals of several hours, were available for study.

In twenty-five cases the earliest electrocardiographic signs of infarction were high T waves, the majority of which became inverted in the healing stage of infarction. In most of the cases the high T waves were no longer present twenty-four hours after the attack. In five instances where the T waves persisted for several days, early mortality was as high as 60 per cent, as compared with 14 per cent in the cases where the high T waves underwent regression within twenty-four hours.

The high T waves are thought to be part of the injury pattern. They were accompanied by abnormal elevations of S-T in twenty-one cases. In five instances elevation of S-T was either absent or within normal range. In one instance huge upright T waves were associated with marked depression of S-T.

In the majority of the cases high T waves preceded the development of significant changes in the QRS complex. The latter usually appeared within twenty-four hours after the onset of symptoms, when the high T waves were already in the regressive stage. In one instance characteristic changes in QRS did not appear until six days after the attack, and in two instances they failed to develop at all.

In five cases high T waves were not associated with abnormal elevation of S-T, nor with significant changes in QRS. Thus, they represented the leading diagnostic sign in the early stage of myocardial infarction.

REFERENCES

1. Wood, F. C., and Wolferth, C. C.: Huge T Waves in Precordial Leads in Cardiac Infarction, Am. Heart J. **9**:706, 1934.
2. Cooksey, W. B.: Discussion of a Paper by A. R. Barnes Before the Central Society for Clinical Research, J. A. M. A. **101**:2148, 1933.
3. Bohning, A., and Katz, L. N.: Unusual Changes in the Electrocardiograms of Patients With Recent Coronary Occlusion, Am. J. M. Sc. **186**:39, 1933.
4. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infraction, Arch. Int. Med. **5**:142, 1929.
5. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, Arch. Int. Med. **22**:8, 1918.
6. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**:244, 1920.
7. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), Heart **14**:195, 1928.
8. Wilson, F. N.: The Electrocardiogram in Diseases of the Coronary Arteries; in Levy, R. L. (editor): Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Company.
9. Johnston, F. D., Hill, J. G. W., and Wilson, F. N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction. II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, Am. Heart J. **10**: 889, 1935.
10. Rothschild, M. A., Mann, H., and Oppenheimer, B. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Artery Occlusion, Proc. Soc. Exper. Biol. & Med. **23**:253, 1926.
11. White, P. D.: Heart Disease, New York, 1944, The Macmillan Company.
12. Levine, S. A.: Clinical Heart Disease, Philadelphia and London, 1945, W. B. Saunders.
13. Ashman, R., and Hull, E.: Essentials of Electrocardiography, New York, 1941, The Macmillan Company.
14. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea and Febiger.
15. Stewart, C. B., and Manning, G. W.: A Detailed Analysis of the Electrocardiograms of 500 R. C. A. F. Aircrew, Am. Heart J. **27**:502, 1944.
16. Deeds, D., and Barnes, A. R.: The Characteristics of the Chest Lead Electrocardiograms of 100 Normal Adults, Am. Heart J. **20**:261, 1940.
17. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1000 Healthy Aviators, Am. Heart J. **27**:524, 1944.
18. Buechner, F.: Deutung des Elektrokardiogramms bei den Durchblutungsstoerungen des Herzmuskels, Klin. Wchnschr. **17**:1713, 1938.
19. Master, A. M., Gubner, R., Dack, S., and Jaffee, H. L.: Differentiation of Acute Coronary Insufficient With Myocardial Infarction From Coronary Occlusion, Arch. Int. Med. **67**:647, 1941.
20. Bailey, R. H.: The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle, Am. Heart J. **31**:677, 1946.
21. Wolferth, C. C., Bellet, S., Livezey, M. M., and Murphy, F. D.: Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationship to Positive Displacement; An Experimental Study, Am. Heart J. **29**:220, 1945.
22. Bailey, R. H., La Due, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, Am. Heart J. **27**:164, 1944.

ELECTROLYTE CHANGES AND THE ELECTROCARDIOGRAM IN DIABETIC ACIDOSIS

HELEN EASTMAN MARTIN, M.D., AND MAXINE WERTMAN, A.B.
LOS ANGELES, CALIF.

THE changes in the electrocardiogram in diabetic acidosis are well known since the report and review of Bellet and Dyer,[1] and consist of depression of the S-T segment, lengthening of the Q-T interval, and alterations in the amplitude and direction of the T waves. The fact that these changes are reversible and the electrocardiogram reverts to normal after several days has strongly suggested that alterations in electrolyte balance are important factors in the production of the abnormalities.

METHOD AND MATERIAL

The study to be reported was undertaken to see if there was any correlation between pH, calcium, potassium, and magnesium levels and the electrocardiographic changes. No previous similar complete electrolyte study has been reported to our knowledge. Thirteen patients who entered the hospital in severe diabetic acidosis (carbon dioxide combining power under 9 milliequivalents, calculated as bicarbonate) were followed for several days with synchronous determinations of blood chemistry and electrocardiograms. The chemical determinations in all patients included serum calcium, potassium, sodium, and magnesium levels, total plasma protein, blood sugar, and carbon dioxide combining power. In order to calculate the ionized calcium fraction, additional studies in five patients included the determination of the albumin and globulin fraction and blood pH. A detailed report of the results and methods, including the formula used for calculation of the ionized calcium value, has been described elsewhere.[2] The Q-T interval for each electrocardiogram was calculated by the formula of Ashman[3] with the corrections suggested for age and sex.

RESULTS

The results of the electrolyte changes correlated with the electrocardiographic changes are summarized in Table I. The relationships of the various changes are analyzed separately in Tables II to VI.

Table II summarizes the correlation between the depression of the S-T segment and acidosis. When present, the depression of the S-T segment, with a

From the Department of Medicine of the University of Southern California School of Medicine and the Los Angeles County Hospital.
Received for publication April 10, 1947.

straight upsweep into the T wave, occurred usually during the first twenty-four hours. It was felt, therefore, that this factor might be related to acidosis. In nineteen instances of depressed S-T segment, the carbon dioxide combining power or pH was low in sixteen, or 84 per cent. Of the twenty-nine instances of isoelectric S-T segments, twenty, or 69 per cent, were associated with normal pH and carbon dioxide combining power, while nine, or 31 per cent, occurred with low pH or low carbon dioxide combining power. The depressed S-T segments which occurred when there was acidosis returned to the isoelectric line at the same time that the acidosis was corrected (Cases 2, 4 to 6, 8, 9, 12, and 13, and Table I). It is to be noted that in our series of diabetic patients there was no definite correlation between the level of the serum potassium and depression of the S-T segment. (This is contrary to the experimental work in dogs,[4] where depression of the S-T segment occurred with moderate elevation of the serum potassium levels.) Further studies will be necessary to establish the mechanism of this change in the S-T segments.

Table III summarizes the results of total serum calcium and potassium levels, as correlated with the Q-T interval, in eight patients. Twenty-two records showed prolonged Q-T intervals, and of this group only four had low calcium levels and one a low potassium concentration.

With the shifts in pH and total protein which occur during the therapy of diabetic acidosis, it was felt that the level of ionized calcium might not always follow the total calcium concentration, and that this factor might be important in the prolongation of the Q-T interval. Table IV gives the relationship between total and ionized serum calcium values in five patients. Of twenty-five total serum calcium concentrations only four were abnormal, while fifteen of the calculated ionized values were below normal. Also, the ionized calcium fraction represented a variable fraction of the total serum calcium concentration (39 to 52 per cent).

Table V shows the results of these detailed studies of total calcium, ionized calcium, and potassium in five patients. In eighteen determinations of the Q-T interval, five were markedly prolonged, twelve were slightly prolonged, and one was normal. In ten instances, these abnormalities were associated with decreased ionized calcium levels, and four, in addition, showed low potassium concentrations. In six instances, slightly prolonged Q-T intervals were associated with normal serum calcium, total and ionized fraction, and normal serum potassium levels.

Summarizing Tables III and V, there were thirty-seven records with prolonged Q-T intervals. In sixteen, or 43 per cent, of these the total or ionized calcium and potassium (one or all) were below normal; while in twenty-one, or 57 per cent, of the records with prolonged Q-T interval, the total and ionized calcium and potassium were within the normal range at the time the record was made. It is to be noted, however, that of the seven records with markedly prolonged Q-T intervals, in six abnormalities of calcium or potassium levels, or both, were present when the records were made. These facts suggest that in over 50 per cent of the instances of prolonged Q-T interval there was some

TABLE I. GENERAL SUMMARY OF RESULTS

DAY	HOUR	pH	MEQ. HCO_3	MEQ. Ca	MEQ. Ca++	MEQ. Mg	MEQ. K	CYCLE LENGTH	Q-T INTERVAL	CALCULATED Q-T INTERVAL	S-T SEGMENTS	T_1	T_2	T_3	TCF_4
1. A. B., White Man, 69 Years of Age, No. 723-522															
1	2	7.28	10.0	4.35	2.15	1.47	5.38	.60	.32	.31	Isoelectric	Isoelectric	▲ Low	▲ Very low	▲ Slightly low
1	20	7.60	24.0	4.30	2.20	1.06	1.90	.75	*	.35	Isoelectric	Isoelectric	Diphasic; very low	▼ Very low	▲ Very low
2	1	7.65		4.40	2.20	1.39	2.77	.71	*	.34	Isoelectric	Isoelectric	▲ Very low	▲ Almost isoelectric	▲ Very low
2	20	7.63		4.30	2.15	1.47	2.18	.75	*	.35	Isoelectric	Isoelectric	▲ Very low	▲ Almost isoelectric	▲ Very low
3		7.59		4.25	2.15	1.39	3.36	.74	*	.35	Isoelectric	Isoelectric	▲ Almost isoelectric	▲ Almost isoelectric	▲ Very low
4		7.60		4.45	2.20	1.56	5.13	.91	.43	.38	Isoelectric	▲ Very low	▲ Normal	▲ Low	▲ Normal
5		7.57		4.40	2.30	1.23	6.64	.81	.39	.36	Slight elevation of $S\text{-}T_2$ and $S\text{-}T_3$	▲ Very low	▲ Slightly low	▲ Slightly low	▲ Slightly low
6		7.52		4.75	2.30	1.31	4.31	.80	.40	.36	Isoelectric	▲ Very low	▲ Slightly low	▲ Slightly low	▲ Slightly low
7		7.55		4.50	2.25	1.39	6.13	.77	.40	.35	Isoelectric	Isoelectric	▲ Very low	▲ Very low	▲ Very low
2. T. B., Colored Woman, 19 Years of Age, No. 683-113															
1	0	7.05	7.5	5.25	2.15	1.98	6.72	.41	.28	.26	Depressed	▲ Rapid rise, low	▲ Rapid rise, low	▲ Low	▲ Low
1	6	7.29	9.5	4.65	2.05	1.16	5.42	.49	.34	.29	Very slight depression	▲ Slightly low	▲ Slightly low	▼ Low	▲ Normal
2		7.55	22.0	4.80	2.20	0.56	3.20	.82	.51	.37	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
3		7.55		4.70	2.25	1.40	4.56	.84	.43	.37	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
4		7.58		5.00	2.25	1.48	4.56	.90	.42	.38	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal

3. N. W., White Woman, 44 Years of Age, No. 319-307

1	20	7.58	17.0	3.85	1.60	0.82	3.41	.58	.38	.32	Isoelectric	▲ Low	▲ Normal	▲ Slightly low	▲

4. B. M., White Man, 19 Years of Age, No. 968-418

1	2	7.12	7.0	5.70	2.25	2.13	7.28	.43	.28	.26	Isoelectric I, sagging II and III, slight elevation IV	▲ Normal	▲ Rapid rise, slightly low	▲ Rapid rise, very low	▲ Very high (12 mm.)
1	9	7.51	18.5	4.65	2.05	1.56	5.00	.48	.29	.28	Isoelectric	▲ Low	Diphasic—low	▼	▲ Normal
2		7.58		4.40	2.05	1.23	5.74	.63	.36	.32	Isoelectric I and III, slight elevation II and IV	▲ Normal	▲ Low	▼	▲ Normal
5		7.51	26.0	4.85	2.10	1.47	5.64	.71	.31	.33	Slight elevation II, III, IV	▲ Normal	▲ Low	▼ Low	▲ Normal

5. E. S., White Woman, 19 Years of Age, No. 962-393

1	10	7.32	4.9	5.20	2.45	1.56	4.26	.41	*	.24	Depressed	▲ Rapid rise, ? low	▲ Rapid rise, low	▼	▼
1	13	7.49	16.5	5.00	2.40	1.31	2.20	.44	*	.27	Depressed	▲ Rapid rise, very low	▲ Rapid rise, very low	? ▼ Low	▼ Low
1	16	7.64	23.0	5.15	2.30	1.39	2.18	.43	*	.27	Depressed	▲ Rapid rise, very low	▲ Rapid rise, very low	▼	▼ Low
2		7.51	17.5	4.90	2.30	1.88	3.85	.59	.46	.32	Very slightly depressed	▲ Very low, broad	▲ Very low, broad	▼ Low	▲ Low
4		7.32		3.55	1.85	1.15	3.49	.52	.32	.30	Isoelectric	▲ Very low	▲ Normal	▲ Normal	▲ Normal
37		7.33		4.95	2.05	1.39	6.18	.59	.35	.32	Slight elevation S-T_2 and S-T_3	▲ Normal	▲ High	▲ Normal	▲ Normal

6. R. B., White Man, 40 Years of Age, No. 950-958

1	2		<4.5	5.55		2.95	5.11	.52	.37	.29	Sagging	▲ Rapid rise, normal	▲ Normal	▲ Normal	▲ Normal
6		•		4.45		1.39	4.98	.72	.37	.34	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
13				4.65		1.23	5.54	.73	.36	.34	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal

TABLE I. GENERAL SUMMARY OF RESULTS—(CONT'D)

DAY	HOUR	pH	MEQ. HCO_3	MEQ. Ca	MEQ. Ca++	MEQ. Mg	MEQ. K	CYCLE LENGTH	Q-T INTERVAL	CALCULATED Q-T INTERVAL	S-T SEGMENTS	T_1	T_2	T_3	TCF_4
7. F. C., White Boy, 12 Years of Age, No. 211-641															
1	3		9.0	5.25		2.46		.43	.27	.26	Isoelectric	▲ Rapid rise, low	▲ Rapid rise, low	Isoelectric	▲ Normal
4			8.0	4.45		1.56	4.87	.63	.34	.32	Isoelectric	▲ Low, broad	▼ Low	▼	▼
10				3.95		1.06	4.26	.73	.38	.34	Isoelectric	Isoelectric	▼	▼	▼
21				4.80		1.35	7.20	.56	.29	.30	Isoelectric	▲ Normal	▲ Normal	▼	▲ Low
38				5.50		1.39	5.87	.61	.32	.30	Isoelectric	▲ Normal	▲ Normal	▼	▲ Low
8. E. R., White Man, 40 Years of Age, No. 949-632															
1	20		19.5	4.30		0.98	3.82	.48	.34	.28	Sagging $S\text{-}T_1$ and $S\text{-}T_2$	▼ Low	▼ Low	Isoelectric	▼
8				4.40		1.48	5.08	.74	.40	.34	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
9. J. S., White Woman, 18 Years of Age, No. 866-215															
1	0		5.5	5.50		2.46		.50	.35	.29	Sagging	▲ Rapid rise, low	▲ Rapid rise, low	▲ Rapid rise, low	▼ ?
1	20		21.5	3.85		1.52		.71	.37	.34	Isoelectric	▲ Low	▲ Low	Isoelectric	▲ Low
5				5.65		1.23		.63	.35	.33	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal

10. M. K., White Boy. 16 Years of Age, No. 947-988

1	2		5.5	5.25		2.21		.48	.34	.28	Isoelectric	↑ Normal	↓	↓	↑
1	21		20.5	4.95		1.39		.50	.33	.28	Isoelectric	↑ Broad—low	Isoelectric	↓	↑
7				5.20		1.72	5.84	.81	.40	.35	Isoelectric	↑ Normal	↑	↓	↑ Normal

11. J. W., White Boy, 13 Years of Age, No. 949-854

1	0		<4.5	5.15		1.56		.47	.32	.27	Isoelectric	↑	↓ ?	↓	↑
1	19		14.0	5.45		1.23	3.52	.64	*	.32	Isoelectric	Broad, low	Low, wide	Very low	↑ Normal
6				4.85		1.31	5.67	.62	.36	.31	Isoelectric	↑ Normal	↑ Normal	↑ Normal	↑ Normal

12. T. A., White Boy, 17 Years of Age, No. 34-034

1	4		6.5	4.15		1.83	5.57	.46	.32	.27	Sagging	↑ Slightly low	↑ Rapid rise, very low	↓	↑
2				4.00		0.98	4.36	.65	.36	.32	Isoelectric, S-T_1 and S-T_2, slight elevation III	↑ Slightly low	Isoelectric	↓ Low	↑ Slightly low
3				4.40		1.23	5.93	.57	.36	.30	Isoelectric	↑ Normal	↑ Low	↓	↑ Normal

13. A. D., White Woman, 39 Years of Age, No. 954-618

1	3		12.5	4.40		1.11	4.26	.60	.33	.32	Slight sagging S-T_2 and S-T_3	↑ Very low	↑ Low	↑ Low	↑ Low
2				4.55		1.31	7.21	.71	.40	.34	Isoelectric	↑ Normal	↑ Normal	↑ Low	↑ Low

If the carbon dioxide combining power is not given after the first 24 hours, this was because it had become normal, and was not checked further in most instances.
*Unable to calculate.

factor other than serum calcium and potassium responsible. It is possible that the normal range of Q-T interval may not be wide enough, even when corrected for age or sex. Some undetermined factor which persists for several days or weeks may also be present following severe diabetic acidosis. It is seen from Table I that in most instances, even after four or five days, most of the Q-T intervals are still slightly prolonged.

TABLE II. ACIDOSIS AND THE S-T SEGMENT CHANGES

pH DETERMINATIONS (FIVE PATIENTS)		
pH LEVEL	DEPRESSED S-T SEGMENT	ISOELECTRIC S-T SEGMENT
7.0–7.25	2	0
7.25–7.35	2	3
7.35–7.65	3*	15
CO_2 COMBINING POWER (THIRTEEN PATIENTS)		
CO_2 C. P.	DEPRESSED S-T SEGMENT	ISOELECTRIC S-T SEGMENT
0-10 meq.	8	4
10-20 meq.	4	2
20+ meq.	0	5

*These values were all in the same patient and did not check closely with the CO_2 combining power.

TABLE III. CORRELATION OF CALCIUM AND POTASSIUM CONCENTRATION WITH Q-T INTERVAL (EIGHT PATIENTS)

SERUM LEVELS CA AND K	Q-T INTERVAL		
	MARKEDLY PROLONGED	SLIGHTLY PROLONGED	NORMAL
Ca and K both normal	1	10	1
Ca low, K normal	1	2	
K low, Ca normal		1	
Only Ca determined:			
Normal		4	
Low		1	

One of the most striking changes in the electrocardiogram in diabetic acidosis is the occurrence of abnormal T waves, particularly very low or isoelectric waves. As seen in Table VI, in ten records with very low T waves nine were associated with very low serum potassium levels. Insulin is known to cause a definite decrease in serum potassium levels and urinary excretion.[2,5,6,8] This was found to occur most strikingly in the first twenty-four hours of intensive insulin therapy and has been reported in detail elsewhere.[2] As the serum potassium concentra-

*These values were all in the same patient and did not check closely with the CO_2 combining power.

TABLE IV. CORRELATION OF IONIZED AND TOTAL CALCIUM CONCENTRATIONS (FIVE PATIENTS)

PATIENT	TOTAL Ca CONCENTRATION (MEQ.)	CALCULATED IONIZED Ca (MEQ.)	PER CENT OF TOTAL CALCIUM AS [ca++]
A. B.	4.45	2.20	49
	4.40	2.30	52
	4.75	2.30	48
	4.50	2.25	50
T. B.	5.25	2.15	46
	4.65	2.05	44
	4.80	2.20	46
	4.70	2.25	48
	5.00	2.25	45
N. W.	3.85	1.60	42
B. M.	5.70	2.25	39
	5.10	2.00	39
	4.65	2.05	44
	4.40	2.05	47
	4.85	2.10	43
E. S.	5.20	2.45	47
	5.00	2.40	48
	5.15	2.30	45
	4.90	2.30	47
	3.55	1.85	52
	4.95	2.05	41

TABLE V. CORRELATION OF TOTAL AND IONIZED CALCIUM LEVELS AND POTASSIUM LEVELS WITH Q-T INTERVAL (FIVE PATIENTS)

	MARKEDLY PROLONGED	SLIGHTLY PROLONGED	NORMAL
Total and ionized Ca and K normal		6	
Total Ca and K normal; ionized Ca low	2	5	1
Total Ca normal; [Ca++] and K low	1		
Low total and ionized Ca; low K	1	1	
Total and ionized Ca normal; low K	1		

TABLE VI. CORRELATION OF T-WAVE CHANGES WITH SERUM POTASSIUM LEVELS

	NORMAL AMPLITUDE OF T WAVES	DECREASED AMPLITUDE OF T WAVES	VERY LOW TO ISOELECTRIC T WAVES	HIGH T WAVES
Normal serum K levels (4.2-5.8 meq.)	14	12	1	
Low serum K levels (under 4.2 meq.)	1	1	9	
High serum K levels (over 5.8 meq.)	3			1

tion returned to normal levels, the T waves increased in amplitude in most instances. Normal or moderately low T waves were associated with normal potassium values. High T waves occurred in a few patients and were associated with elevated potassium levels. No examples of intraventricular block were seen.

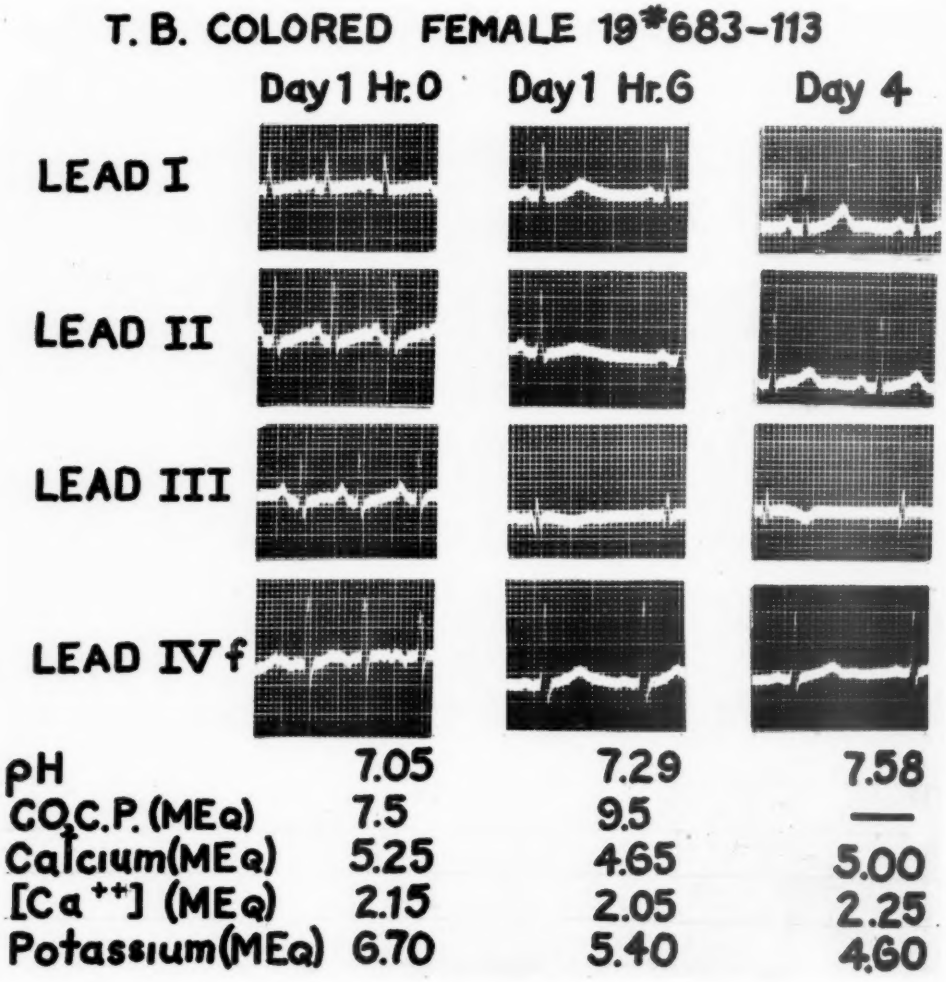


Fig. 1.—Case 2 of Table I. See text for discussion.

The relationship of the magnesium levels to the electrocardiographic changes must remain unsettled, as there have been no studies in the experimental animal on the effect of low magnesium levels on the electrocardiogram. Very low levels were reached in some of our patients, and even after four to seven days the values had not always returned to the normal level for the method used in this laboratory. While a few moderately elevated values of serum magnesium

were obtained, they were not associated with any specific electrocardiographic change. They were not in the range known to produce conduction changes.

Serum sodium levels, even with parenteral therapy, remained relatively constant. It was felt, therefore, that this ion did not enter into the problem of the electrocardiographic changes.

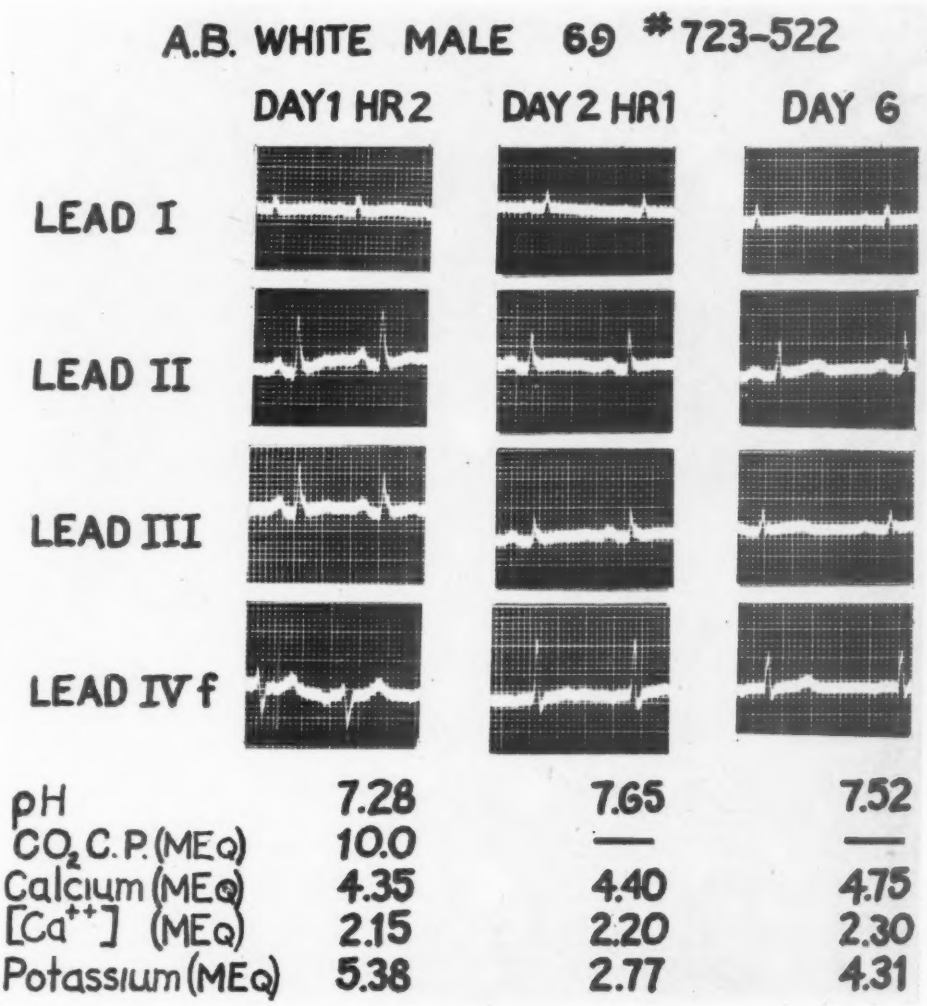


Fig. 2.—Case 1 of Table I. See text for discussion.

Relatively few and insignificant changes occurred in amplitude or character of the P wave or the QRS complex. In only one instance was there a shift in axis deviation during therapy.

The only precordial lead taken in these studies was CF_4. No changes were noted in this lead which were not shown by the indirect leads.

The findings discussed in the preceding material are illustrated in more detail by the electrocardiograms and electrolyte changes in four patients (Figs. 1-4). In Fig. 1, (Case 2, T. B., Table I) Tracing 1, taken on entry before any treatment, shows a striking sagging of the S-T segments with a straight rise into

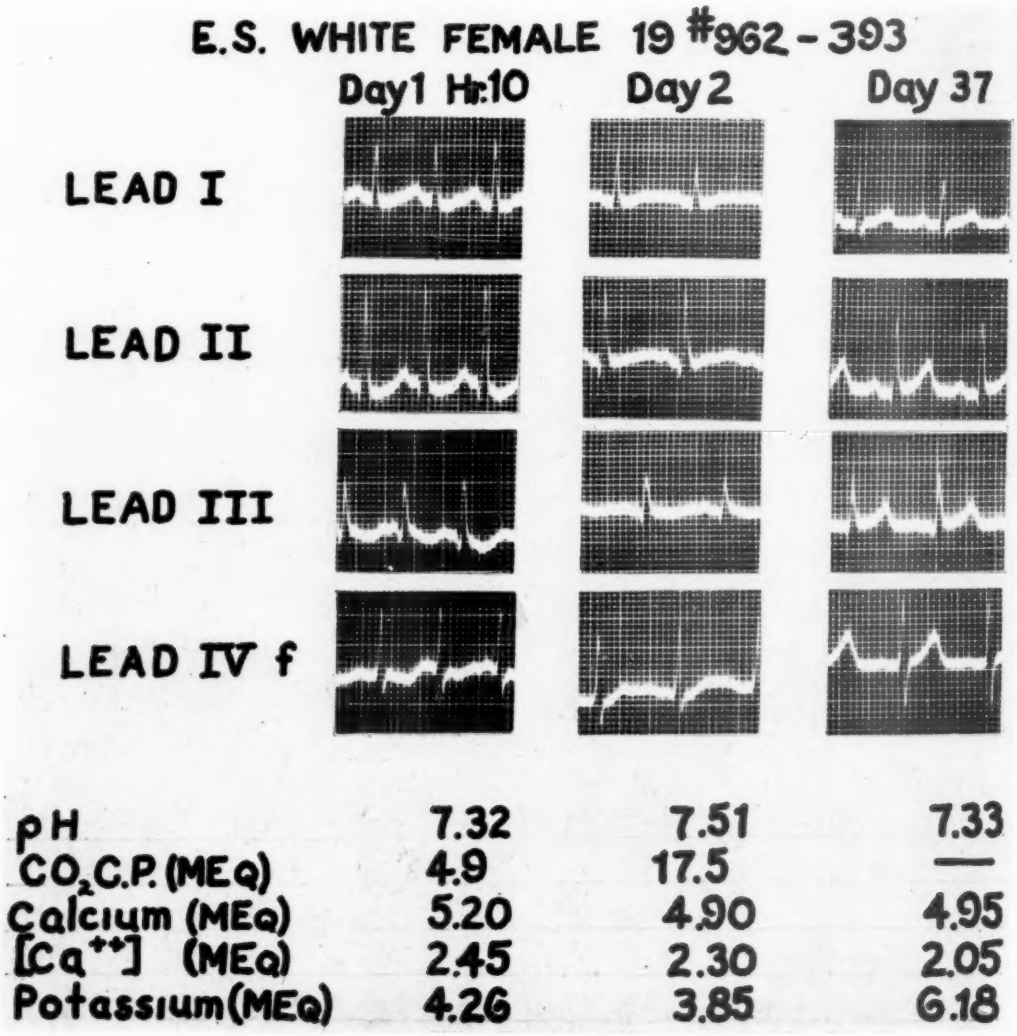


Fig. 3.—Case 5 of Table I. See text for discussion.

low amplitude T waves in the standard leads, plus a marked tachycardia. At this time the pH was 7.05 and serum potassium 6.70 milliequivalents. Six hours later (Fig. 1, Tracing 2), following intensive treatment, the pH had risen to 7.29 (carbon dioxide combining power still only 9.5 milliequivalents; serum potassium 5.40 milliequivalents) and the sagging of the S-T segments is seen to

have disappeared. At this time (six hours after entry) T_2 is broad and the Q-T interval is prolonged (0.34 second, with a calculated normal of 0.288 second), although the serum levels of total calcium and potassium were normal. The ionized calcium was definitely below normal, however (2.05 milliequivalents).

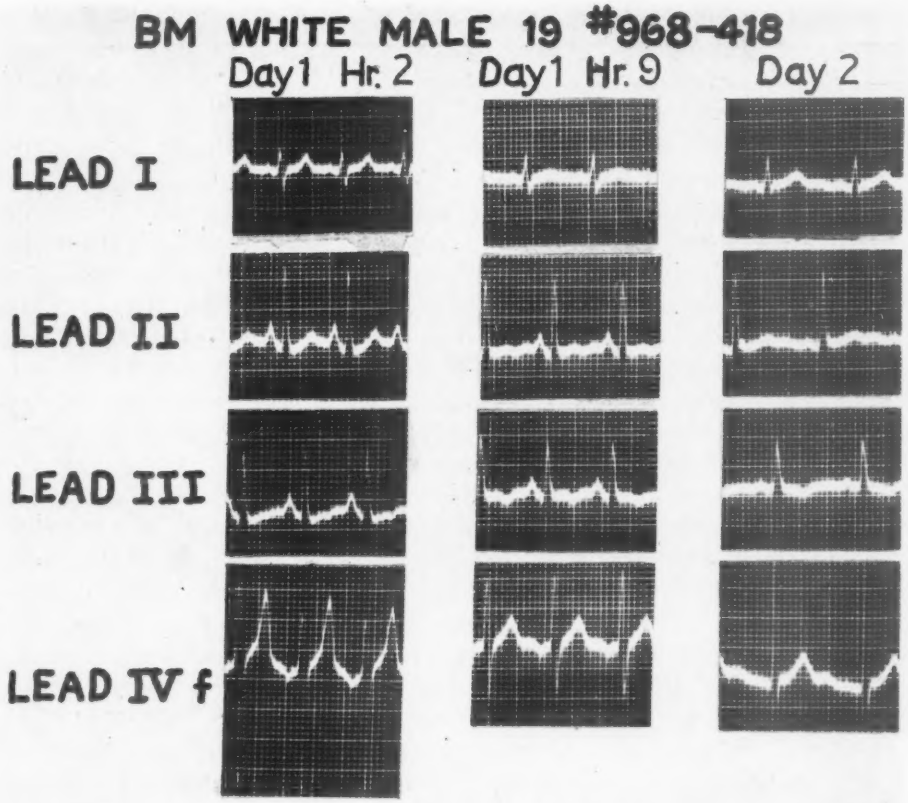


Fig. 4.—Case 4 of Table I. See text for discussion.

By the fourth day the electrocardiogram was entirely normal except for slight prolongation of the Q-T interval and the electrolytes were essentially normal except for slight decrease in serum magnesium.

In Fig. 2 (Case 1, A. B., Table I) the first tracing, taken two hours after entry, shows no sagging of the S-T segment. When this tracing was made there

was only moderate acidosis (pH 7.28) and the potassium concentration was in the normal range (5.38 milliequivalents). The Q-T interval is seen to be normal, as were total serum calcium and potassium concentrations. The ionized calcium was slightly reduced. The second tracing, taken twenty hours after entry, shows a marked reduction in the amplitude of the T waves, which was associated with a drop in the serum potassium from 5.38 to 2.77 milliequivalents. With return of the potassium to normal (4.31 milliequivalents), the T waves increase in amplitude (Day 6, Tracing 3). At this time the only abnormality in the electrocardiogram is a long Q-T interval (0.43 second, with a calculated normal of 0.38 second). All chemistry was normal except for slight reduction of the ionized calcium and magnesium levels.

Fig. 3 (E. S., Case 5, Table I) shows many striking changes. The first tracing, taken ten hours after entry, illustrates depression of the S-T segment with a rapid rise into low amplitude T waves in Leads I and II. At this time the pH was 7.32, and the serum potassium was normal (4.26 milliequivalents). On the second day (second tracing) the T waves are broad and flat and the potassium level had decreased (3.85 milliequivalents). The Q-T interval is definitely prolonged (0.46 second as contrasted to a calculated value of 0.32 second). The serum calcium values, total and ionized, were within the normal range. Tracing 3, taken on the thirty-seventh day, shows a marked increase in amplitude of the T waves, associated with an elevated serum potassium level (6.18 milliequivalents). The Q-T interval is still slightly prolonged (0.35 second as contrasted to a calculated normal of 0.32 second).

Fig. 4 (B. M., Case 4, Table I) shows very high T waves in the fourth lead of Tracing 1 taken two hours after entry, sagging of the S-T segments in Leads II and III, and a prominent S_1. At this time, the serum potassium concentration was definitely elevated (7.28 milliequivalents). Tracing 2, taken nine hours after entry to the hospital, shows a decrease of the T wave in Lead CF_4 to normal amplitude, associated with a normal serum potassium level (5 milliequivalents). Tracing 3, taken two days after entry, is essentially normal with disappearance of S_1; the electrolytes were normal except for decreased ionized calcium and magnesium.

DISCUSSION

The problem of the pathogenesis of the electrocardiographic changes in diabetic acidosis is complex. There are several factors which may be responsible:

1. Changes in pH and extracellular electrolytes.

2. Changes in intracellular electrolytes due to (a) changes in extracellular electrolytes, (b) nutritional state of the muscle due to anoxia, lack of vitamins, and depletion of cardiac glycogen, and (c) effect of retention of waste products due to impaired renal function.

3. Alterations in the rate and depth of breathing associated with the Kussmaul type of respiration, shifts in diaphragm levels secondary to abdominal distention, and the character of the respiratory effort.

The fact that changes in pH and serum calcium and potassium do cause changes in the electrocardiogram is shown by our results in diabetic acidosis, and in a variety of experimental and clinical conditions.

The electrolyte and pH changes produced experimentally or occurring in certain diseases produce definite and specific electrocardiographic changes. In the alkalosis produced by hyperventilation[9] or by the ingestion of sodium bicarbonate[10] there may be decrease in the amplitude of the T waves with late inversion. In the acidosis of exercise or ammonium chloride ingestion[10] there may be increase in the amplitude of the T waves. In both acidosis and alkalosis there may be a slight increase in the length of the Q-T interval. Changes in serum calcium levels have long been known to affect the electrocardiogram.[11,12] The low levels seen in tetany[12] cause striking increases in the Q-T interval, while short Q-T intervals are found associated with the high blood calcium levels of hyperparathyroidism.[13] Changes in serum potassium levels have also been demonstrated to affect the electrocardiogram, both in the experimental procedures in animals and in disease entities.[4-7,11-19] Low levels of serum potassium seen in familial periodic paralysis,[16] in diabetic acidosis,[7] after injection of excessive amounts of desoxycorticosterone acetate,[15] and in chronic nephritis[17] cause low T waves in the electrocardiogram. High serum potassium levels found after injection of potassium[4,14] or in nephritis[19] may conversely be associated with high T waves. With higher levels of serum potassium in animals definite changes occur at certain concentrations: depression of the S-T segment at 8 to 10 milliequivalents per liter, intraventricular block at 10 milliequivalents per liter, disappearance of the P waves at 9 to 10 milliequivalents per liter, and, finally, cardiac arrest at 14 to 16 milliequivalents per liter.[4] Increase in the length of the Q-T interval has also been correlated with low serum potassium levels.[20] The studies on the effect of magnesium on the electrocardiogram have been limited almost exclusively to high levels. Increases in serum magnesium in man and animals cause depression of conduction and depression of abnormal foci of irritability.[21,22]

The relationship of the shifts of extracellular electrolytes to the changes in the intracellular electrolyte pattern is complex and largely an unexplored field. Yannet and Darrow[23] have shown in cats that changes in serum potassium levels are not always accompanied by proportional shifts in intracellular levels in muscle. Also, decreases in serum sodium concentrations are not accompanied by evidence of shift of water into the cells, or of loss of univalent base from the cells. In rats[24] sodium may partially replace potassium intracellularly in conditions of potassium depletion. In certain clinical states there appears to be a discrepancy between serum and intracellular levels. In familial periodic paralysis the serum potassium levels may be low, with postulated normal or increased intracellular levels as the urinary excretion decreases.[25] Further complicating this problem is the possible factor of lag in the balance between extra- and intracellular water and electrolytes.

In diabetic acidosis, before therapy, with lack of enough effective insulin, the problem arises concerning the nutrition of cardiac muscle. In the mammalian

heart-lung preparation, Barnes and associates[26] have shown that heart muscle is capable of direct oxidation of fat to the extent of at least two-thirds of its total metabolic requirement. Visscher and Muller[27] and Cruickshank[28] have also demonstrated in the heart-lung preparation that insulin is not necessary for the utilization of carbohydrate and does not increase glucose utilization. In rats, Evans[29] has shown that cardiac glycogen is not further increased by adding insulin to the glucose injection. These facts all suggest that cardiac nutrition may not be seriously altered during diabetic acidosis. The relationship of vitamin B to carbohydrate utilization in the muscle is well known. As many diabetic patients entering the hospital in acidosis show evidences of vitamin deficiency, this lack may contribute to nutritional changes in cardiac muscle. The relation of these changes to those observed in the electrocardiogram must remain speculative. Hypoglycemia has been shown to alter the electrocardiogram.[30] Suggested possible mechanisms are changes in blood pressure and coronary blood flow, cardiac glycogen, or serum potassium levels. As hypoglycemia was rarely present in our series, this factor cannot be considered significant in the serial changes in the electrocardiogram.

Anoxia experimentally produced in dogs[31] causes changes in the height of the R wave due primarily to increase in the girth of the chest in expiration. Changes in the T waves appeared to be of cardiac origin. Serial changes in the height of the R wave were insignificant in our patients. More important is the fact that the serial changes in the electrocardiogram occurred whether shock was absent or present. The possibility of the effect on the electrocardiogram of waste products arising as a result of impaired renal function secondary to hemoconcentration and shock must be considered. In uremia, the electrocardiographic changes have been fairly well correlated with changes in serum electrolytes, particularly potassium, or with associated pericarditis. The electrocardiographic changes in diabetic acidosis are often most striking after the therapy of the first twenty-four hours, when the nonprotein nitrogen levels are usually normal. Also the serial changes occurred in patients who had no elevation of the nonprotein nitrogen.

The alterations caused by deep breathing and changes in diaphragm level[32] may play a minor role. The changes found do not coincide well with those attributed to these factors. Many of the changes also occurred in patients following cessation of Kussmaul breathing. Abdominal distention also was not always present.

In the last analysis it is the state of the heart muscle which causes alterations in the electrocardiogram. What these intimate changes in the functional chemical state of the cardiac muscle are must remain speculative. That they are related in part to changes in the serum electrolytes has been demonstrated by this and other studies.

SUMMARY

Correlation of electrolyte and pH changes with serial electrocardiographic changes was made in thirteen patients during therapy for severe diabetic acidosis.

Sagging of the S-T segments was a prominent feature of the electrocardiogram on entry when acidosis was marked. This change usually disappeared within twenty-four hours. In nineteen instances of depressed S-T segment, the pH or carbon dioxide combining power was low in sixteen (84 per cent). However, in 31 per cent of the patients whose records showed isoelectric S-T segments, the pH or Carbon dioxide combining power was low. Experimentally, depression of the S-T segment occurs with moderate elevation of the serum potassium but there was no correlation in our series with changes in serum potassium levels. The etiology of this change requires further study.

Thirty-seven records showed prolonged Q-T intervals, many of these occurring one to four days after intensive therapy had been instituted. Sixteen (43 per cent) of these were associated with low total or ionized serum calcium or potassium. Twenty-one (57 per cent) of the patients whose records showed prolonged Q-T intervals had normal levels of serum calcium and potassium. There were seven patients in whom the Q-T interval was markedly prolonged; in six of these the serum calcium or potassium levels were below normal. These findings suggest that in some cases other factors than serum calcium and potassium depletion may be responsible for the prolongation of the Q-T interval.

There was a high degree of correlation between low T waves and low serum potassium levels. The T waves increased in amplitude with return of the potassium to normal or elevated levels.

The relationship of low serum magnesium to the electrocardiographic changes needs additional study.

The complex nature of the factors present in diabetic acidosis which may affect the myocardium is discussed. These factors include the relationship between extracellular and intracellular electrolytes, cardiac nutrition in acidosis and ketosis, and the effects of anoxia and azotemia.

REFERENCES

1. Bellet, Samuel, and Dyer, W. Wallace: The Electrocardiogram During and After Emergence From Diabetic Coma, Am. Heart J. **13**:72, 1937.
2. Martin, Helen Eastman, and Wertman, Maxine: Serum Potassium, Magnesium and Calcium Levels in Diabetic Acidosis, J. Clin. Investigation **26**:217, 1947.
3. Ashman, Richard: The Normal Duration of the Q-T Interval, Am. Heart J. **23**:522, 1942.
4. Winkler, Alexander W., Hoff, Hebbel E., and Smith, Paul K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**:478, 1938.
5. Harrop, George A., Jr., and Benedict, Ethel M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, J. Biol. Chem. **59**:683, 1924.
6. Atchley, Dana W., Loeb, Robert F., Richards, Dickinson W., Jr., Benedict, Ethel M., and Driscoll, May E.: Diabetic Acidosis. A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy, J. Clin. Investigation **12**:297, 1933.
7. Holler, Jacob W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, J. A. M. A. **13**:1186, 1946.
8. Briggs, A. P., Koechig, Irene, Doisy, Edward A., and Weber, Clarence J.: Some Changes in the Composition of Blood Due to the Injection of Insulin, J. Biol. Chem. **58**:72, 1924.
9. Thompson, William Paul: The Electrocardiogram in the Hyperventilation Syndrome, Am. Heart J. **25**:372, 1943.
10. Barker, Paul S., Shrader, Ethel, and Renzoni, Ethel: The Effects of Alkalosis and of Acidosis Upon the Human Electrocardiogram, Am. Heart J. **17**:169, 1939.

11. White, Paul D., and Mudd, Seeley, G.: Observations on the Effect of Various Factor on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, J. Clin. Investigation **7**:387, 1929.
12. Barker, Paul S., and Wilson, Frank N.: The Duration of Systole in Hypocalcemia, AM. HEART J. **14**:82, 1937.
13. Kellogg, Frederick, and Kerr, W. J.: Electrocardiographic Changes in Hyperparathyroidism, AM. HEART J. **12**:346, 1936.
14. Chamberlain, F. L., Scudder, J., and Zwemer, R. L.: Electrocardiographic Changes Associated With Experimental Alterations in Blood Potassium in Cats, AM. HEART J. **18**:458, 1939.
15. Darrow, Daniel C., and Miller, Herbert C.: The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate, J. Clin. Investigation, **21**:601, 1942.
16. Stewart, Harold J., Smith, J. James, and Milherat, Ade T.: Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis, Am. J. M. Sc. **199**:789, 1940.
17. Brown, Madelaine R., Currens, James H., and Marchand, John F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting From Potasisum Loss in Chronic Nephritis, J. A. M. A. **124**:545, 1944.
18. Keith, Norman M., Burchell, H. B., and Baggenstoss, Archie A.: Electrocardiographic Changes in Uremia Associated With a High Concentration of Serum Potassium, AM. HEART J. **27**:817, 1944.
19. Finch, Clement A., Sawyer, C. Glenn, and Flynn, John M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1**:337, 1946.
20. Wofford, Charles I., and Ernstene, A. Carlton: The Diagnostic Significance of an Increased Q-T Interval in the Electrocardiogram, Cleveland Clin. Quart. **8**:12, 1941.
21. Szekely, P.: The Action of Magnesium on the Heart, Brit. Heart J. **8**:115, 1946.
22. Smith, Paul K., Winkler, Alexander W., and Hoff, Hebbel E.: Electrocardiographic Changes and Concentration of Magnesium in Serum Following Intravenous Injections of Magnseium Salts, Am. J. Physiol. **126**:720, 1939.
23. Yannet, Herman, and Darrow, Daniel C.: The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle, Liver and Cardiac Muscle, J. Biol. Chem. **134**:721, 1940.
24. Miller H. C., and Darrow, D. C.: Relation of Muscle Electrolyte to Alterations in Serum Potassium and to Toxic Effects of Injected Potassium Chloride, Am. J. Physiol. **130**: 747, 1940.
25. Allott, E. N., and McArdle, B.: Further Observations on Familial Periodic Paralysis, Clin. Sc. **3**:229, 1938.
26. Barnes, R. H., MacKay, E. M., Mae, G. K., and Visscher, M. B.: The Utilization of Beta-Hydroxybutyric Acid by the Isolated Mammalian Heart and Lung, Am. J. Physiol. **123**:272, 1938.
27. Visscher, Maurice B., and Muller, Erich A.: The Influence of Insulin Upon the Mammalian Heart, J. Physiol. **62**:341, 1926.
28. Cruickshank, E. W. H.: Cardiac Metabolism, Physiol. Rev. **16**:597, 1936.
29. Evans, Gerald: The Effect of Insulin on Cardiac and Liver Glycogen, Am. J. Physiol. **134**:798, 1941.
30. Middleton, W. S., and Oatway, W. H.: Insulin Shock and the Myocardium, Am. J. M. Sc. **181**:39, 1931.
31. Harris, A. Sidney, and Randall, Walter C.: Mechanisms Underlying Electrocardiographic Changes Observed in Anoxia, Am. J. Physiol. **142**:452, 1944.
32. White, Paul D., Chamberlain, Francis L., and Graybill, Ashton: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart, Brit. Heart J. **3**:233, 1941.

COMPARATIVE STUDY ON THE USE OF THE PURIFIED DIGITALIS GLYCOSIDES, DIGOXIN, DIGITOXIN, AND LANATOSIDE C, FOR THE MANAGEMENT OF AMBULATORY PATIENTS WITH CONGESTIVE HEART FAILURE

ROBERT C. BATTERMAN, M.D., AND ARTHUR C. DEGRAFF, M.D.
NEW YORK, N. Y.

CONSIDERABLE attention has been focused upon the use of purified digitalis glycosides. There is no question that their use offers certain advantages over the digitalis leaf. Since the glycoside is a chemical entity, the physician is assured uniform potency regardless of the lot prescribed. In contrast to this, digitalis leaf must be submitted to controlled bio-assay, the results of which, although indicative of relative potency, cannot be directly applied to man.

As experience was gained in the use of the purified glycosides, it became evident that their potency, when used clinically, bore no relationship to the cat unit potency. If the latter was the basis of dosage, there was no way of predicting, except by clinical trial, whether a particular glycoside would produce results similar to that of digitalis leaf. Most likely severe toxicity would occur. It, therefore, became imperative that each glycoside should undergo extensive clinical trial in order to establish its relative potency and to determine satisfactory methods of dosage. In the hands of well-qualified cardiologists the use of purified glycosides offers no particular difficulty. However, unless precise directions are available and their pharmacology firmly established, the use of the purified glycosides by the general practitioner may not be satisfactory. It is for this reason that an extensive program for the evaluation of purified glycosides has been in progress by us and co-workers for the past ten years. Several reports[1] have already appeared on various phases of the glycoside problem, but to date we have avoided any reference to selection of any particular glycoside as the one of choice. This report deals with a comparative study of the use of the three glycosides, digoxin, digitoxin, and lanatoside C, in the treatment of the ambulatory patient.

The management of the patient with congestive heart failure may be considered as a twofold problem. The importance of the initial digitalization, regardless of the method used, is self-evident. However, in terms of digitalis potency or comparative potencies of the various glycosides, it is not the major problem. The patient can be readily digitalized, regardless of the potency of

From the Department of Therapeutics, New York University College of Medicine, and the New York University Cardiovascular Clinic.
Received for publication Jan. 31, 1947.

the preparation used, as long as repeated doses are administered. One should, of course, take into account absorbability and rapidity of dissipation of the digitalis preparation. Since, in our opinion, the maintenance of the digitalized state is the most important aspect of the management of the patient with congestive heart failure, this study was instituted to determine the following for each glycoside: (1) the daily undivided dose most likely to result in satisfactory maintenance; (2) the daily undivided dose most likely to result in minimal signs and symptoms of toxicity; (3) the therapeutic ratio; (4) the relative ease of establishment of satisfactory maintenance with control of congestive heart failure and ventricular rate; and (5) the ease of predicting the maintenance dose when initiating this dose in a patient who has been previously rapidly digitalized or who had been receiving another digitalis preparation.

SCOPE OF INVESTIGATION

The study was conducted on ambulatory patients. All required the daily administration of a digitalis preparation to be maintained in a state of satisfactory compensation. The cessation of digitalis, therefore, or improper maintenance would immediately result in the development of signs and symptoms of congestive heart failure. None of the patients required supplementary diuretic therapy, and if at any time their use became necessary, the patient was no longer followed for maintenance studies. Seventy-four patients, diagnosed according to the criteria of the New York Heart Association,[2] composed the study group. The diagnostic data are presented in Table I. Patients with recent

TABLE I. DIAGNOSIS AND HEART RHYTHMS OF AMBULATORY PATIENTS TREATED WITH GLYCOSIDES

		NUMBER OF PATIENTS
Diagnosis		
Rheumatic heart disease		38
Mitral stenosis and insufficiency	28	
Mitral stenosis and insufficiency and aortic insufficiency	6	
Mitral stenosis and insufficiency and aortic stenosis and insufficiency	4	
Arteriosclerotic heart disease		13
Arteriosclerotic and hypertensive heart disease		10
Hypertensive heart disease		5
Syphilitic heart disease		2
Rheumatic and hypertensive heart disease		1
Unknown heart disease		2
Unknown and hypertensive heart disease		1
Unknown and hyperthyroid heart disease		2
Total		74
Rhythm		
Auricular fibrillation		52
Normal sinus rhythm		22
Total		74

myocardial infarction, with frequent episodes of anginal syndrome, or other medical conditions which may have either altered the cardiac status or interfered with proper evaluation of therapy were excluded.

METHOD

With few exceptions, the patients had been previously observed for months or years on a standard digitalis leaf preparation (U. S. P. X to XII) so that their digitalis requirements were well known. The initial dose level of the glycoside* substituted for the digitalis leaf was arbitrarily chosen as any multiple of the smallest tablet furnished by the pharmaceutical concern. Regardless of the dose, the patient was advised to take the entire amount as an undivided dose, preferably at the same time each day. As experience was gained in the use of glycosides, it became evident that this was very important for proper maintenance. A division of the dose over a twelve- to sixteen-hour period would have resulted in accentuation of the dissipation factor which interfered with proper evaluation of the dose level. A supply of the glycoside was dispensed at each clinic visit to last until the next examination. The visits were at intervals of between two and five weeks but were usually at intervals of three weeks. If the patient failed to keep an appointment or if the dose of the glycoside was not taken regularly, the trial was discarded and a new period of observation begun. A minimum period of eight weeks of observation on each dose level was established because it became evident that it might require this time for the full cumulative effects of single daily doses to achieve maximum action. The patient was, therefore, observed for a trial period of at least eight to ten weeks, usually three clinic visits, on each dose level. The only exception to this rule was when a particular dose resulted in toxicity or was definitely unsatisfactory for maintenance and the patient's welfare demanded an immediate change of dosage. At the end of a suitable period of observation, an electrocardiogram was taken and another dose level instituted. An attempt was made to determine the minimal dose for either satisfactory maintenance or developments of signs and symptoms of toxicity by either decreasing or increasing the daily dose by small increments.

RESULT

It was possible to evaluate digoxin for a total of 119 trials in forty patients; digitoxin for 103 trials in thirty-two patients, and lanatoside C for 133 trials in forty-six patients. The number of patients receiving each glycoside or combination of glycosides is presented in Table II. We were fortunate in being able to follow sixteen patients over a sufficient length of time to allow studies on all three glycosides. Complete studies with establishment of both minimal maintenance and toxic doses are available in ten of these patients.

---

*_Digoxin_ was supplied by Burroughs Wellcome & Co., Inc., New York, N. Y., in 0.25 mg. tablets. _Digitoxin_ was supplied by Varick Pharmacal Co., Inc., New York, N. Y., under the trade name Digitaline Nativelle, in tablets of 0.1 and 0.2 mg. _Lanatoside C_ was supplied by Sandoz Chemical Works, Inc., New York, N. Y., under the trade name Cedilanid, in 0.5 mg. tablets.

TABLE II. NUMBER OF PATIENTS TREATED WITH EACH GLYCOSIDE OR COMBINATION OF GLYCOSIDES

Total number of patients	74
Patients receiving digoxin	40
Established maintenance dose	30
Established toxic dose	28
Established both	22
Patients receiving lanatoside C	46
Established maintenance dose	34
Established toxic dose	34
Established both	27
Patients receiving digitoxin (Digitaline Nativelle)	32
Established maintenance dose	26
Established toxic dose	31
Established both	26
Patients receiving all three glycosides	16
Complete studies available	10
Comparisons of maintenance dose	12
Comparisons of toxic dose	13
Patients receiving digoxin and lanatoside C	25
Complete studies available	15
Comparisons of maintenance dose	17
Comparisons of toxic dose	19
Patients receiving digoxin and digitoxin	20
Complete studies available	14
Comparisons of maintenance dose	17
Comparisons of toxic dose	17
Patients receiving lanatoside C and digitoxin	16
Complete studies available	12
Comparisons of maintenance dose	13
Comparisons of toxic dose	14

TABLE III. EFFECTIVENESS OF VARIOUS DAILY ORAL DOSES OF DIGOXIN

DOSE (MG.)	TRIALS	NUMBER OF PATIENTS			
		WELL MAINTAINED	FAIRLY WELL MAINTAINED	DEVELOPED INCREASED CONGESTIVE HEART FAILURE	DEVELOPED TOXICITY
0.25	17	9	5	3	0
0.5	30	15	6	7	2
0.75	29	11	4	5	9
1.00	20	13	3	0	4
1.25	12	5	1	0	6
1.5	7	3	0	0	4
1.75	3	1	0	0	2
2.0	1	0	0	0	1
Total	119	57	19	15	28

Studies With Digoxin.—Experiences with the various dose levels are summarized in Table III. It is apparent that there is considerable individual variation. A daily undivided dose of 1.0 mg. would have resulted in toxicity in fifteen of thirty-one patients (48.4 per cent), but in sixteen of twenty patients in whom this dose was tried, maintenance was satisfactory. The maintenance dose of digoxin was established in thirty patients (Table IV) and ranged be-

TABLE IV. DAILY UNDIVIDED DOSE OF DIGOXIN REQUIRED FOR EITHER MAINTENANCE OR TOXICITY

DOSE (MG.)	NUMBER OF PATIENTS	
	MAINTENANCE	TOXICITY
0.25	9	
0.50	7	2
0.75	5	9
1.00	6	4
1.25	2	6
1.50	1	4
1.75	0	2
2.00	0	1
Total	30	28

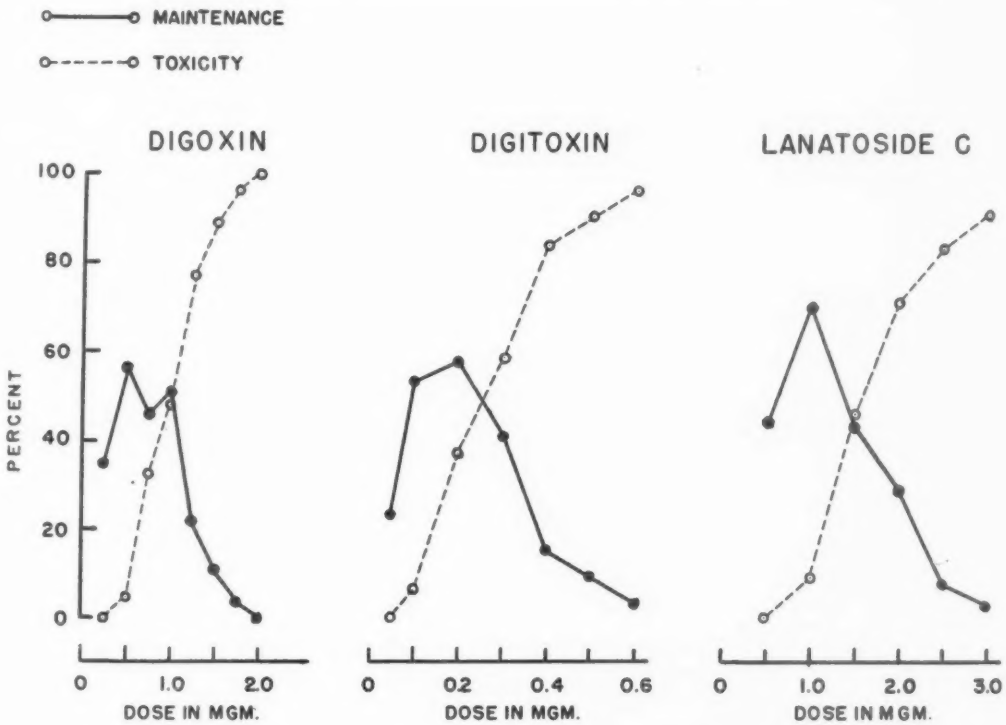


Fig. 1.—Per cent of patients presenting either maintenance or toxicity with the daily administration of various doses of digoxin, digitoxin, and lanatoside C.

tween 0.25 and 1.5 mg., the dose roughly parallelling the severity of the underlying heart disease. Seventy per cent of the patients were maintained with a dose of 0.75 mg. or less. The toxic dose for daily administration ranged between 0.5 and 2.0 mg. and was established in twenty-eight patients (Table IV). Approximately 60 per cent of the patients had toxicity with an undivided dose of 1.0 mg. or above. Fig. 1 represents the predictability of achieving maintenance or toxicity with any daily dose level and indicates that the dose of choice when initiating maintenance with digoxin, if no knowledge of previous digitalis leaf dosage is available, is 0.5 milligrams. This dose will be effective in the greatest number of patients with the least possibility of toxicity. A daily undivided dose of 1.0 mg. has an equal chance of either maintaining the patient or producing toxicity. If the patient has been previously receiving digitalis leaf, digoxin could be substituted in doses of 0.5 mg. for each 0.1 Gm. of digitalis leaf (U. S. P. XII). In all cases the minimal maintenance dose was established without difficulty. This was accomplished in spite of the rapid dissipation of digoxin. The latter interfered with proper maintenance only if the daily dose was divided.

Studies With Digitoxin.—Results with digitoxin are summarized in Tables V and VI and Fig. 1. Fifty per cent of the patients were maintained with a daily dose of 0.1 mg. or less. The toxic daily dose was noted from 0.1 mg. upward but was usually encountered above 0.2 milligram. Thus, approximately 61 per cent of the patients manifested toxicity with a dose of 0.3 mg. or above. As in the case of the other glycosides, considerable individual variation was noted. The maintenance dose ranged between 0.05 and 0.3 milligram. The dose which appears to be the best for selection when the patient requires maintenance for the first time would be 0.1 milligram. This dose will maintain the majority of the patients, while the likelihood of toxicity is very small. The daily administration of 0.2 mg. resulted in toxicity in 37.5 per cent of the pa-

TABLE V. EFFECTIVENESS OF VARIOUS DAILY ORAL DOSES OF DIGITOXIN

DOSE (MG.)	TRIALS	NUMBER OF PATIENTS			
		WELL MAINTAINED	FAIRLY WELL MAINTAINED	DEVELOPED INCREASED CONGESTIVE HEART FAILURE	DEVELOPED TOXICITY
0.05	10	6	1	3	0
0.1	23	11	3	7	2
0.2	29	15	3	1	10
0.3	20	12	1	0	7
0.4	13	4	1	0	8
0.5	5	3	0	0	2
0.6	3	1	0	0	2
Total	103	52	9	11	31

TABLE VI. DAILY DOSE OF DIGITOXIN REQUIRED FOR EITHER MAINTENANCE OR TOXICITY

DOSE (MG.)	NUMBER OF PATIENTS	
	MAINTENANCE	TOXICITY
0.05	6	0
0.1	7	2
0.2	11	10
0.3	2	7
0.4	0	8
0.5	0	2
0.6	0	2
Total	26	31

tients. The maintenance and toxic doses were established without any difficulty with the exception of one patient who could not tolerate any dose. The smallest size tablet used was 0.1 milligram. With the administration of 0.1 mg. every other day (0.05 mg. per day), adequate maintenance was obtained in seven patients (24 per cent). It is, therefore, recommended that digitoxin should be made available in 0.05 mg. tablets.

Studies With Lanatoside C.—Results with lanatoside C are summarized in Tables VII and VIII and Fig. 1. The maintenance dose ranged between 0.5 and 3.0 milligrams. Approximately 62 per cent of the patients were maintained with a daily undivided dose of 1.0 milligram. Toxic effects were noted with 1.0 mg. or more and were usually encountered with a dose greater than 1.5 mg., toxicity occurring in 28 per cent of the patients with this dose or above. Again, there was considerable overlapping of doses and individual variations. This was particularly so for the 1.5 mg. dose. From Fig. 1 it can be seen that there is an equal chance of either producing maintenance or toxicity with this dose.

TABLE VII. EFFECTIVENESS OF VARIOUS DAILY ORAL DOSES OF LANATOSIDE C

DOSE (MG.)	TRIALS	NUMBER OF PATIENTS			
		WELL MAINTAINED	FAIRLY WELL MAINTAINED	DEVELOPED INCREASED CONGESTIVE HEART FAILURE	DEVELOPED TOXICITY
0.5	27	12	4	11	0
1.0	39	20	5	10	4
1.5	35	10	6	5	14
2.0	20	9	1	1	9
2.5	8	3	0	1	4
3.0	4	1	0	0	3
Total	133	55	16	28	34

TABLE VIII. DAILY UNDIVIDED DOSES OF LANATOSIDE C REQUIRED FOR EITHER MAINTENANCE OR TOXICITY

DOSE (MG.)	NUMBER OF PATIENTS	
	MAINTENANCE	TOXICITY
0.5	12	0
1.0	9	4
1.5	6	14
2.0	5	10
2.5	1	3
3.0	1	3
Total	34	34

The most satisfactory dose for initiating maintenance would be 1.0 mg. daily. It was definitely more difficult to establish a maintenance dose with lanatoside C than with the other glycosides. This was reflected in the relatively higher number of trials, 21 per cent of which resulted in congestive heart failure as compared with 12.6 per cent and 10.7 per cent for digoxin and digitoxin, respectively (Table X). In seven patients establishment of the maintenance dose was particularly difficult since the patients were in congestive heart failure with one dosage level and developed toxicity with the next dosage level. In several instances the patient's condition did not allow further studies with lanatoside C since it was obvious that the maintenance dose would not be established with any degree of certainty in a suitable period of time to benefit the patient. In such cases it became necessary to change to digitalis leaf or another glycoside.

Comparative Studies in the Same Patient.—Complete studies for maintenance and toxicity dose for all three glycosides are available on ten patients. These are summarized in Table IX. In general, the relative potency for each glycoside was the same for each patient. If the patient could be maintained with a small dose of one glycoside, the patient could be mantained with a small dose of the other two glycosides. The same relative potency held also for the toxic dose. With one exception (Patient S. S.) the therapeutic range of all glycosides was not too dissimilar.

Therapeutic Ratio.—The therapeutic ratios for the three glycosides were identical. When the minimal maintenance dose was doubled, toxicity occurred with digoxin in 63.6 per cent of the patients, with digitoxin in 65.4 per cent, and with lanatoside C in 62.9 per cent.

Toxic Manifestations.—With daily doses that produced toxicity, the signs and symptoms were the same for all three glycosides as far as type and incidence were concerned. They differed from those noted with digitalis leaf in two respects. It was unusual for diarrhea to be noted as a toxic symptom for any of the glycosides. Visual disturbances were just as common but did not include yellow or green vision. Occasional patients noted alteration in color vision with

emphasis on objects appearing white. Although the impression was gained that gastrointestinal irritation was less with the use of the glycosides, it is impossible for us to state with certainty that this is significant. In our experience the usual small doses of digitalis leaf administered for maintenance rarely result in true gastrointestinal irritation. If a patient develops nausea and vomiting with digitalis leaf, it is invariably the result of central toxicity and the same symptoms would occur for each glycoside if comparable doses were administered.

TABLE IX. COMPARATIVE DAILY MAINTENANCE AND TOXIC DOSES IN THE SAME PATIENT FOR DIGOXIN, DIGITOXIN, AND LANATOSIDE C

PATIENT	DIGOXIN		DIGITOXIN		LANATOSIDE C	
	M. D.* (MG.)	T. D.† (MG.)	M. D. (MG.)	T. D. (MG.)	M. D. (MG.)	T. D. (MG.)
J. M.	1.0	1.5	0.2	0.4	2.0	2.5
S. S.	0.25	0.75	0.05	0.2	1.5	1.5
F. L.	1.0	2.0	0.2	0.3	1.5	2.0
N. P.	0.25	0.75	0.1	0.4	1.0	2.0
C. S.	0.5	0.75	0.1	0.2	1.5	2.0
F. B.	0.75	1.75	0.2	0.5	1.5	2.5
G. G.	0.25	0.75	0.1	0.2	0.5	1.5
A. H.	0.25	0.5	0.05	0.1	0.5	1.5
M. M.	1.0	1.25	0.1	0.2	2.0	2.5
Z. P.	0.5	0.75	0.2	0.2	1.0	2.0

*M. D., Maintenance dose.
†T. D., Toxic dose.

TABLE X. COMPARATIVE SUMMARY OF THE AMBULATORY USE OF DIGOXIN, DIGITOXIN, AND LANATOSIDE C

	DIGOXIN	DIGITOXIN	LANATOSIDE C
Daily undivided dose most likely resulting in maintenance	0.5 mg.	0.1 mg.	1.0 mg.
Daily undivided dose most likely resulting in toxicity	1.0 mg.	0.2-0.3 mg.	1.5-2.0 mg.
Patients presenting toxicity on doubling minimal maintenance dose	63.6%	65.4%	62.9%
Number of trials resulting in poor maintenance regardless of dose	12.6%	10.7%	21%
Ease of achieving maintenance	Good	Good	Fair
Ease of predicting dose	Good	Good	Trial and error
Dissipation	Rapid	Slow	Rapid
Duration of Toxicity	Short	Long	Short

The glycosides differed, however, in the duration of toxicity. Whereas it was unusual for the signs and symptoms of toxicity to persist longer than forty-eight hours for either digoxin or lanatoside C, in many instances the toxicity following digitoxin persisted for seventy-two to ninety-six hours or even a week. Furthermore, in adjusting the dose of the glycoside following the occurrence of

toxicity, it was absolutely imperative to stop the administration of digitoxin for several days. In the case of lanatoside C or digoxin, the patient could easily continue on a smaller dose or even the same total dose, but in divided amounts, and yet have all signs and symptoms of toxicity subside very promptly.

DISCUSSION

The most important advantage of the introduction of purified digitalis glycosides is their uniformity from lot to lot. The physician is assured that the potency of any glycosides will always be the same and that maintenance, when established, will not vary because of uncontrolled factors inherent in the preparation.

With the exception of an occasional patient who cannot tolerate digitalis leaf because of local gastrointestinal irritation and the psychologic factor of prescribing digitalis, the use of the purified glycosides does not offer any other advantage over digitalis leaf. Purified glycosides will not result in a more efficient or safer digitalization. The patient will not be maintained any more effectively. If a patient is no longer satisfactorily maintained with digitalis leaf and toxicity occurs with the next dosage level, the substitution of a purified glycoside will result in the same response if comparable doses are used. In other words, the glycosides may vary in terms of latency of action, speed of dissipation, and degree of gastrointestinal absorption, but they appear to be identical as far as their action upon improving the efficiency of heart muscle is concerned. Furthermore, the toxic manifestations, although differing in duration, appear to be generally the same for the purified glycosides and digitalis leaf.

In comparing any particular glycoside with any other, the same relative potencies held for both maintenance and toxic doses. The therapeutic range for each preparation appears to be the same. However, in the case of lanatoside C, the therapeutic range in some instances appears to be exceedingly small. This is related to factors other than cardiac action and may be explained either by rapidity of dissipation or destruction of the drug in the gastrointestinal tract or by a combination of both of these factors. Evidence in favor of destruction is the relative difficulty encountered in determining the maintenance dose of lanatoside C in respect to digoxin; dissipation studies[3] of both of these glycosides in man are similar. Furthermore, knowing the maintenance dose of digitalis leaf, digitoxin, or digoxin, it was comparatively easy to predict the maintenance dose or interchange of any three of these preparations, whereas for lanatoside C it was a question of trial and error in many cases. This definitely impairs the usefulness of lanatoside C for oral use in maintenance. The usefulness of digitoxin, while satisfactory for maintenance, is offset by its slow rate of dissipation and prolonged toxicity. Furthermore, the dosage forms that are supplied at present, 0.1 and 0.2 mg., do not lend themselves to great freedom in establishing satisfactory maintenance levels. An increase of 100 per cent in dosage of digitoxin is relatively more dangerous than the same increase of digoxin or lanatoside C. For these reasons digoxin appears to be the glycoside of choice for the daily management of the patient with congestive heart failure.

SUMMARY

1. Comparative studies on three purified digitalis glycosides, digoxin, digitoxin, and lanatoside C, were performed in a group of seventy-four ambulatory patients.

2. For reasons of safety in administration and satisfactory maintenance, digoxin is the glycoside of choice.

3. Lanatoside C administered orally is not satisfactory for the routine daily management of the patient with congestive heart failure.

4. Other than the assurance of obtaining uniformity in various lots, the glycosides have no particular advantage over digitalis leaf.

5. The incidence and degree of toxic symptoms is the same for the three glycosides. The duration of toxicity is much greater with digitoxin than with lanatoside C or digoxin.

This study was made possible by the fullest cooperation, financial assistance, and generous supplies of the glycosides by the following Pharmaceutical Companies: Burroughs Wellcome & Co. (U.S.A.) Inc., New York, N. Y.; Lederle Laboratory Division, American Cyanamid Co., Pearl River, N. Y.; Sandoz Chemical Works, Inc., New York, N. Y.; and Varick Pharmacal Co., Inc., New York, N. Y.

REFERENCES

1. (a) Batterman, R. C., Rose, O. A., and DeGraff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, AM. HEART J. **20**: 443, 1940.
   (b) Batterman, R. C., Holman, D. V., and DeGraff, A. C.: The Therapeutic Effectiveness of Potency of Digilanid in the Treatment of Contestive Heart Failure, Ann. Int. Med. **14**:2058, 1941.
   (c) DeGraff, A. C., and Batterman, R. C.: Recent Advances in Digitalis Therapy With Particular Attention to the Use of Pure Glycosides, M. Clin. North America, **26**:929, 1942.
   (d) Rose, O. A., Batterman, R. C., and DeGraff, A. C.: Clinical Studies on Digoxin, a Purified Digitalis Glycoside, AM. HEART J. **24**:425, 1942.
   (e) Eichna, L. W., Taube, H., and DeGraff, A. C.: Serial Determinations of Cardiac Output (Ballistocardiogram) and Electrocardiogram in Normal Man After the Intravenous Administration of Purified Cardiac Glycosides, J. Pharmacol. & Exper. Therap. **78**:22, 1943.
   (f) Eichna, L. W., and Taube, H.: A Comparison of the Actions of Four Cardiac Glycosides on a Patient With Congestive Heart Failure, AM. HEART J. **26**:631, 1943.
   (g) Eichna, L. W., and Taube, H.: The Effect of Intravenously Administered Digoxin and Ouabain on the Systemic Venous Pressure of Patients With Congestive Heart Failure, AM. HEART J. **27**:641, 1944.
   (h) Batterman, R. C., and DeGraff, A. C.: Studies on the Rate of Dissipation and Digoxin in Man, Federation Proc. **4**:112, 1945.
   (i) DeGraff, A. C.: Clinical Comparison of the Cardiac Glycosides, New York State J. Med. **45**:1803, 1946.
2. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York Heart Association, New York, 1939.
3. Unpublished data.

ELECTROCARDIOGRAPHIC CHANGES IN EARLY SYPHILIS

HOWARD P. STEIGER, M.D.,* CHARLOTTE, N. C., AND JOSEPH EDEIKEN, M.D.†
PHILADELPHIA, PA.

IT IS well known that there is a spirochetemia during the early stages of a syphilitic infection. There is, however, considerable difference of opinion as to whether or not the heart is affected during this period. Extensive investigations have been made and the conclusion in most of the later studies is that there is little evidence of cardiovascular involvement in early syphilis.[1-6] The majority of these analyses does not include electrocardiographic studies of the dark-field positive patient before, during, and after treatment. In those cases studied during the course of intensive treatment, the electrocardiographic changes when present were, in most cases, attributed to the toxic effects of the arsenicals upon the myocardium.

Since penicillin shows little evidence of being toxic to the myocardium, and, at the same time, the patients are hospitalized for complete syphilitic treatment, we think the entire subject should be re-evaluated.

Grassmann[7] in 1900 described cardiac arrhythmias and murmurs in patients in various stages of syphilis, and since many of these changes were present prior to treatment and cleared following therapy, they were considered to be due to syphilis. In 1913, Warthin[8] reported finding *Treponema pallidum* in the myocardium of cases of active secondary syphilis. His description of these findings is indeed classic: "Large colonies of spirochetes may be found in the myocardium either in the tissue spaces of certain muscle areas, or about the blood vessels, without any changes in the neighboring heart muscle that can be recognized by any technical methods at the present time. The muscle stains as well as normal heart muscle; it contains no vacuoles or granules and presents all the appearances of normal muscle. The spirochetes lie in the intermuscular spaces, often in great numbers. Sometimes they appear within the muscle substance,

This study is part of the investigations on penicillin in syphilis being conducted under Grant RG-13C from the National Institute of Health. The work is collaborated in and sponsored by the Institute for the Study of Venereal Disease, University of Pennsylvania and U. S. Public Health Service cooperating; by the members of the Penicillin-Syphilis Panel, including Herman Beerman, M.D., George D. Gammon, M.D., Paul Gyorgy, M.D., Norman R. Ingraham, Jr., M.D., John W. Lentz, M.D., William O. LaMotte, M.D., E. K. Rose, M.D., and John H. Stokes, M.D., Director and responsible investigator, and the Edward B. Robinette Foundation, and the Medical Clinic, Hospital of the University of Pennsylvania.

An abstract of this paper was presented at a Symposium on Recent Advances in the Investigation of Venereal Diseases held in Washington, D. C. on April 17, 1947, under the auspices of the Syphilis Study Section of the National Institute of Health.

Received for publication Jan. 14, 1947.

*P. A. Surgeon (R), U. S. Public Health Service.

†Instructor, Department of Medicine, University of Pennsylvania Medical School.

as shown in cross sections, but this is not common. Such findings are most frequent in congenital syphilis, but such collections of spirochetes without recognizable myocardial changes are found in acquired syphilis, particularly in active secondary and early tertiary syphilis."[9] Boyd,[5] however, states that myocardial scars and focal collections of lymphocytes and plasma cells have been attributed to syphilis, but without justification.

Turner and White[6] studied fifty cases of primary and secondary syphilis; forty-nine of these showed normal findings or minor variations which could not be ascribed to any pathologic process. The one case showing changes revealed left axis deviation and rather high P waves in Leads II and III. No significant T-wave changes were found. They concluded that the evidence of cardiovascular involvement in early syphilis was exceedingly rare. On reviewing these cases, however, one is impressed with the fact that all of the cases had received some arsenotherapy prior to the electrocardiographic examination, and that studies were not made for at least two weeks after treatment started. In light of the transient nature of the changes often noted in the study described herewith, it seems entirely possible that these patients were studied after the time during which these changes could have occurred. Arnett[1] reported no significant findings in twenty-four cases of secondary syphilis, but it is not clear as to the amount of treatment these patients had received prior to the electrocardiographic examination. The time interval between treatment and examination also is not stated. Chamberlain and Follows[3] reported fifty-seven cases of early syphilis studied from the cardiac standpoint and found no evidence of myocardial change. Again the question of treatment prior to examination must be raised. Wilson and associates[2] studied twenty cases of primary and secondary syphilis before and after salvarsan and noted no clinical or electrocardiographic evidence of cardiac or aortic involvement. He concluded that recognizable involvement of these organs in early stages of the disease is rare.

Sadusk,[10] in discussing the papers of Leifer and associates and Elliott and associates on massive arsenotherapy, reported inversion of T_3 and diminished amplitude of T_2 in a few cases treated with the five-day arsenoxide drip. Geiger, Craig, and Sadusk[11] described electrocardiographic changes in twenty-one of twenty-five cases (including two cases retreated). These patients, treated with the five-day drip, showed electrocardiographic changes similar to those of this study, except they were not noted prior to treatment. These changes were considered to be toxic manifestations of arsenic and not due to syphilis. Three cases that had received previous arsenotherapy in this series did not show the T-wave changes. Stokes, Beerman, and Ingraham, Jr.,[12] state that as methods for the detection of conduction defects improve, an increased frequency of changes is noted; but whether this increase is due to lesions or disturbances produced by ischemic fibrosis or active spirochete-containing foci is still over the horizon. Klotz and Crede[13] in a series of 100 consecutive cases of primary and secondary syphilis treated with the twenty-day syringe method (approximately 60 mg. of mapharsen daily for twenty days) found four cases with altered T waves when examinations were made before treatment. These abnormalities disappeared following the twenty days of arsenotherapy. Six additional cases

showed low voltage T waves which increased in amplitude at the completion of arsenotherapy. Other minor changes such as ventricular extrasystoles and slightly depressed RS-T segments were noted.

METHOD AND PROCEDURE

Only cases of primary and secondary syphilis with dark-field positive lesions confirmed by at least two experts were selected (Table I). Individuals with a history of heart disease, hypertension, and diabetes were not included. The patients

TABLE I. SUMMARY OF THIRTY CASES OF EARLY SYPHILIS STUDIED. ALL CASES DARK-FIELD POSITIVE FOR TREPONEMA PALLIDUM

NO.	ELECTROCARDIOGRAPHIC ABNORMALITY*		DIAGNOSIS	REMARKS
	BEFORE TREATMENT	DURING TREATMENT		
1	None	Definite	Secondary	Abnormal 7th day† only. See Fig. 1
2	None	None	Secondary	Normal throughout
3	Definite	Definite	Secondary	Varied abnormal to normal for 112 days; normal at 162 days. See Fig. 5
4	Definite	Definite	Secondary relapse	Abnormal 30 days
5	None	None	Seropositive primary	Normal throughout
6	None	Definite	Secondary relapse	Abnormal 3rd to 6th day
7	None	None	Secondary relapse	Normal throughout
8	Definite	Definite	Secondary	Abnormal to 58th day; then normal to 77th
9	None	None	Secondary	Normal throughout
10	None	Definite	Secondary reinfection (?)	Abnormal 3rd day only
11	Definite	Definite	Seronegative primary	Abnormal for 35 days. See Fig. 3
12	None	None	Secondary	Normal throughout
13	None	None	Secondary	Normal throughout
14	Definite	Definite	Secondary	Still abnormal at 97 days. See Fig. 4
15	None	None	Secondary relapse	Normal throughout
16	None	None	Secondary relapse	Normal throughout
17	Definite	Not done	Secondary	No follow-up
18	Questionable	Questionable	Secondary relapse	Low amplitude T waves only
19	Definite	Definite	Seropositive primary	Normal in 11 days. See Fig. 2
20	None	None	Secondary	Normal throughout
21	None	Definite	Secondary relapse	Abnormal 5th day only
22	None	None	Secondary	Normal throughout
23	None	None	Secondary	Normal throughout
24	None	None	Secondary	Normal throughout
25	None	None	Secondary relapse	Normal throughout
26	Definite	Definite	Seronegative primary	Improved 3rd day, regressed on 8th, normal on 30th day
27	Definite	None	Secondary	Abnormal only before treatment
28	Definite	Definite	Secondary relapse	Abnormal throughout
29	Questionable	Questionable	Secondary	Still has low amplitude T waves at 55 days
30	Definite	Definite	Secondary	Abnormal throughout

*For criteria of abnormality see page 677.
†Day—first day of treatment counted as first day.

were hospitalized during treatment and were completely studied from a general standpoint as well as from the cardiologic standpoint prior to treatment and during treatment. The electrocardiograms were taken prior to the institution of penicillin therapy and as near to every three days thereafter as administratively possible. All electrocardiographic determinations were taken with the patient in a sitting position. With the exception of one case who received calcium penicillin in beeswax peanut oil, all patients received penicillin sodium dissolved in normal saline without the addition of procaine. This was given in the gluteal muscle every three hours night and day. The controls were patients with no physical, serologic, or historical evidence of syphilis. These individuals had minor pyogenic infections such as impetigo, etc., and received the same amounts of penicillin as the syphilitic patients.

STUDIES AND OBSERVATIONS

The electrocardiographic abnormalities consisted of T-wave and RS-T segment changes in the limb and/or chest leads; in no instance was there any evidence of interference in conduction.

In addition to inverted and diphasic T waves in Leads I and/or II, T waves in these leads were considered abnormal when upright, but less than 1 mm. in amplitude; in the chest leads, upright T waves less than 2 mm. in amplitude were considered abnormal. The RS-T segment was considered abnormal in the limb leads when displaced upward or downward more than 2 mm.; such changes were common in the chest leads, although as an isolated finding they were not considered abnormal inasmuch as such changes, especially elevation of the RS-T segment, are frequently observed in supposedly normal individuals. A Q_3 wave as an isolated finding was not considered abnormal.

Fifteen (50 per cent) of thirty cases showed abnormalities either before or during treatment; of these, eleven showed definite changes before the start of penicillin treatment and the remainder during treatment. In nine cases the changes involved the T waves in Leads I and II and the chest leads, although in some the abnormalities varied from tracing to tracing, and in three instances the T waves in Lead I were inverted. In three cases T_2 alone showed the most marked abnormality, and in all three the changes were of short duration. In one instance abnormalities were observed in T_2 and the chest leads, and in two cases the chest leads alone disclosed changes. In eight cases the electrocardiogram was observed to return to normal in a period ranging from three days to four months. In one instance (not observed to return to normal after two months) follow-up was not possible because the patient, an English seaman, was forced to leave the country. In those who had showed electrocardiographic abnormalities before treatment, examination failed to reveal any other cause for these changes. The electrocardiographic abnormalities were of several types:

1. In four instances the changes were fleeting (Fig. 1). The T-wave abnormalities were present during only one examination, and it is, therefore, possible that if electrocardiograms were made more frequently than every third

Fig. 1.—Case 1. *A*, Electrocardiogram of white woman, 27 years of age, with secondary syphilis, taken May 29, 1946, before treatment. *B*, Tracing made June 5, 1946, after receiving 1,280,000 units of penicillin. *C*, Tracing made June 8, 1946. Subsequent electrocardiograms showed no changes.

day, a larger percentage of cases may have shown changes. In another case, (Fig. 2) the T-wave abnormalities were present before treatment, and returned to normal within a period of eleven days.

2. Variation in T-wave abnormalities in the same leads were present during repeated examinations as shown in Fig. 3.

3. The leads in which T-wave abnormalities appeared varied in repeated examinations. See Fig. 4.

In an effort to determine whether a particular type of case showed electrocardiographic changes, the available materiai was analyzed further as follows:

Herxheimer Reaction.—It is admitted that other evidences of the Herxheimer reaction or therapeutic shock could occur without temperature elevation or skin manifestations. These reactions, however, were the only evidence used as criteria of Herxheimer reactions in this series.

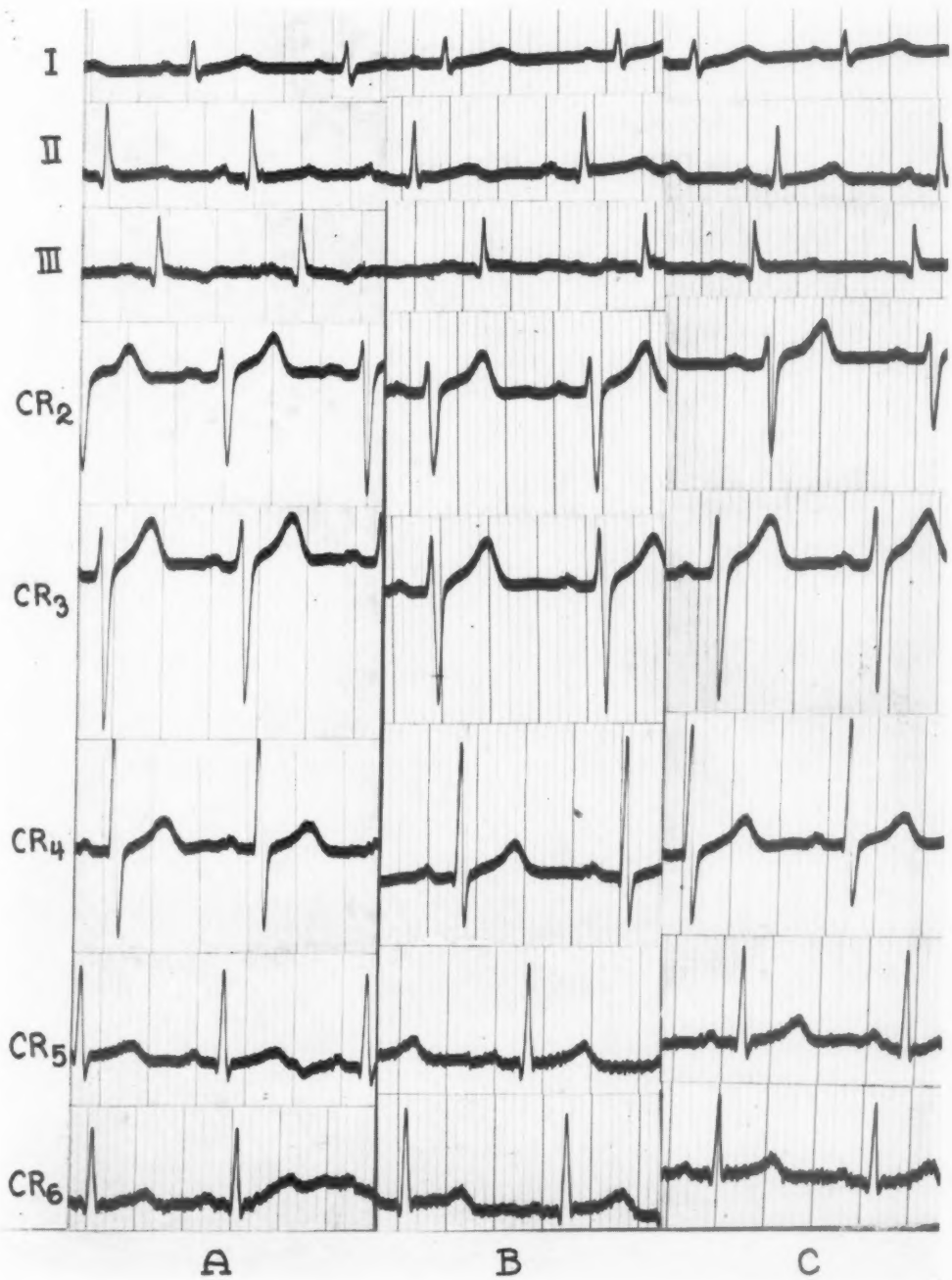


Fig. 2.—Case 19. *A*, Electrocardiogram of white man, 37 years of age, with seropositive primary syphilis, made May 4, 1946, before start of treatment. *B*, Tracing made May 7, 1946, after receiving approximately 480,000 units of penicillin. *C*, Electrocardiograms made May 14, 1946, two days after completion of treatment. All subsequent tracings including those made on readmissions were similar to *C*.

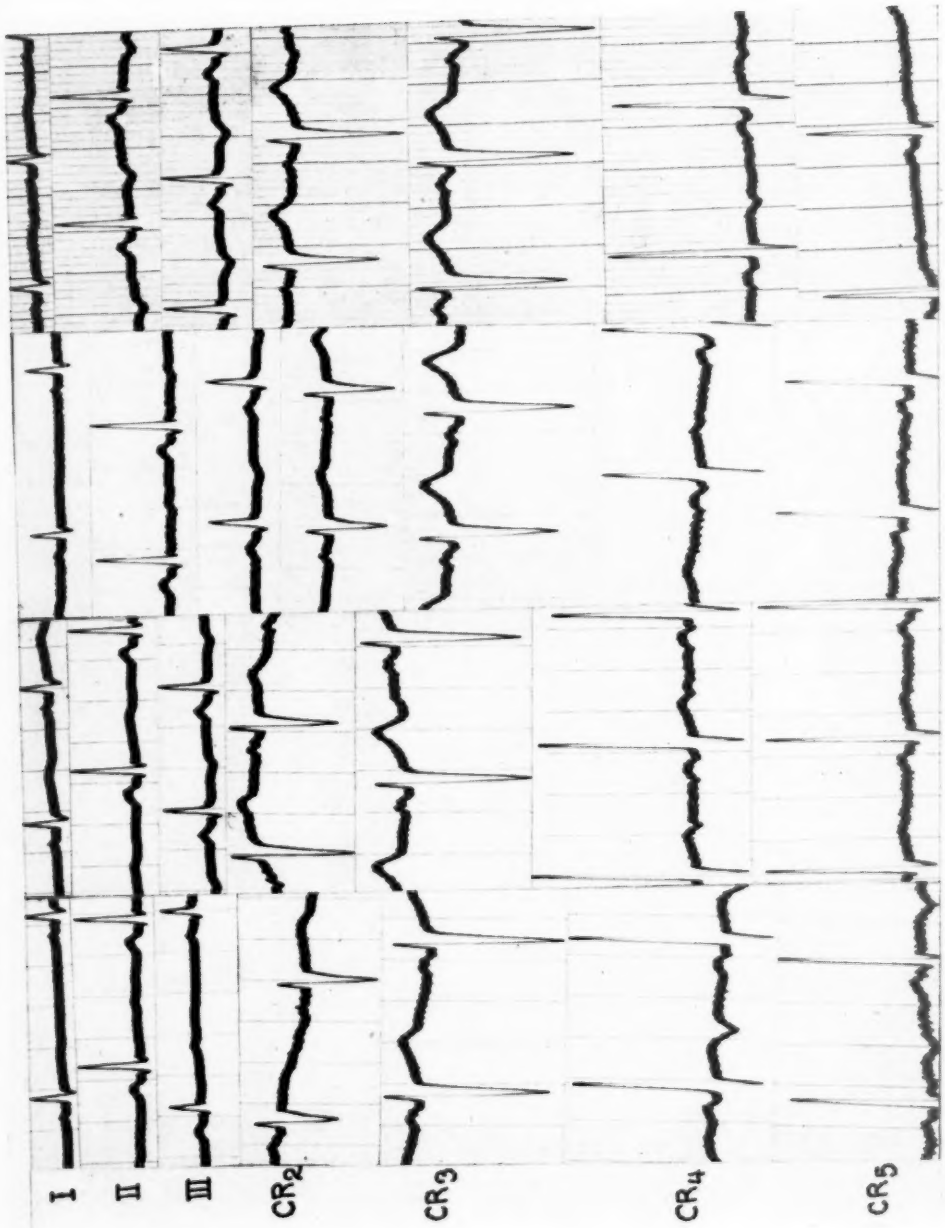


Fig. 3.—Case 11. *A*, Electrocardiogram of white man, 29 years of age, with seronegative primary syphilis, made June 12, 1946, before treatment, which was started on same day. 80,000 units were given every three hours. *B*, Tracing made next day, June 13, 1946. *C*, Electrocardiograms made June 20, 1946, and *D*, tracing made July 2, 1946. All subsequent tracings up to July 16, 1946, when he left the country, were similar to *D*.

July 16, 1946, when he left the country, were similar to *D*.

Fig. 4.—Case 14. *A*, Electrocardiogram of colored man, 47 years of age, admitted to the hospital because of peptic ulcer. During routine examination he was found to have secondary syphilis. The tracing was made July 31, 1946, before treatment. *B*, Electrocardiograms made Aug. 3, 1946, after receiving 960,000 units of penicillin. *C*, Tracing made Aug. 9, 1946, after completion of treatment. *D*, Electrocardiogram made Aug. 12, 1946. A subsequent tracing made Oct. 21, 1946, was similar to *D*.

Eleven patients (37 per cent) showed evidence of a Herxheimer reaction. A sharp elevation in temperature occurring six to eight hours after the initial intramuscular injection was considered a manifestation of the Herxheimer reaction, if the temperature exceeded 100° F. by mouth. Temperatures were taken every four hours and careful notes were made as to the exaggeration of skin lesions during this period. The results are as follows:

Herxheimer reactions (total)	11 (37 per cent)	
Electrocardiographic abnormalities before treatment	11 (37 per cent)	(not including two questionable)
Electrocardiographic abnormalities after and not before	4 (13 per cent)	
Total cases with electrocardiographic changes	15 (50 per cent)	
11 cases—Herxheimer reactions	5 showed electrocardiographic changes (45 per cent)	
19 cases—No Herxheimer reactions	10 showed electrocardiographic changes (53 per cent)	
30		

The difference between 53 per cent showing electrocardiographic changes and no Herxheimer reaction is not significant as compared to 45 per cent of the cases showing electrocardiographic changes and a Herxheimer reaction. There were four cases showing electrocardiographic abnormalities after penicillin when the prepenicillin electrocardiogram was normal. Two of these four cases had clinical Herxheimer reactions.

Age.—The ages of the thirty patients in this study varied from 15 to 47 years. Electrocardiographic abnormalities were distributed throughout without correlation.

Weight.—The subjects varied in weight from 42 kilograms to 165 kilograms; again there was no correlation.

Sex.—Seventeen of the thirty cases were women (57 per cent) and thirteen men (43 per cent). Eight women showed changes as compared to seven men.

Color.—Twenty-four were Negro and six were white; no race difference in the electrocardiographic changes was noted.

Duration of Infection.—

STAGE	CASES	ECG CHANGES
Seronegative primary	2	2
Seropositive primary	2	1
Secondary	15	6
Recurrent lesions*	11	6
	30	15

*Includes relapsing and probable reinfections.

It is interesting to note that changes were present in all phases of early infectious syphilis. The abnormalities in the electrocardiogram, if due to syphilis, seem to occur very early in the infection. Since these changes in some cases were of a very short duration, it is entirely possible that other cases had the same changes and were missed entirely.

Amount of Penicillin.—

14 cases—Initial doses	80,000
15 cases—Initial doses	40,000
1 case —Penicillin beeswax oil, initial dose	150,000

Four cases showing changes after treatment and not before

3 cases—Initial doses	40,000
1 case —Initial dose	80,000

Since the majority of the cases which showed T-wave abnormalities had the changes before penicillin was administered, the dose of penicillin would not enter into the development of electrocardiographic changes. Four cases, however, did show electrocardiographic abnormalities after treatment when the prepenicillin examination had been negative. Three of these four were started on 40,000 units and the other on 80,000 units of sodium penicillin. Since 15 (50 per cent) of this series of thirty cases received an initial dose double that of the remainder, and only one receiving the larger dose showed electrocardiographic abnormalities after treatment, additional evidence is lent to the probability that penicillin is not the cause of these changes.

In light of the evidence of a neurotropic spirochete, we immediately were confronted with the possibility that one strain of spirochete may cause these changes. There were four pairs of patients, each of whom, we were reasonably sure, was infected by the same strain. The results are as follows:

Case 7 and Case 22, husband and wife; neither showed changes

Case 8 and Case 9, sisters infected by the same man; Case 8 showed changes and Case 9 was normal

Case 25 and Case 26, husband and wife; husband, Case 25, was normal and Case 26 showed changes

Case 13 and Case 18, husband and wife; husband, Case 18, was questionable and wife, Case 13, was normal

Although these cases were treated in different stages, and it is entirely possible that changes could have been present and missed, it is interesting to note the marked difference in involvement in these cases, probably involving the same spirochete.

Previous Treatment.—All cases were dark-field positive at the time of the initial electrocardiographic examination. Seven cases, however, gave histories of previous antisyphilitic therapy. In no case could we definitely prove a reinfection, so these cases are simply classified as recurrent lesions.

Three individuals (43 per cent) in the seven with a history of previous treatment showed changes. Twelve cases (52 per cent) of the twenty-three who had no previous treatment showed electrocardiographic abnormalities.

Type of Infection.—Twenty-eight of these thirty patients had cerebrospinal fluid examinations. These, however, were done during the first six days of treatment, and none before penicillin was started. Two of the twenty-eight cases showed positive spinal fluids; Case 14 showed a type II fluid, and Case 30 showed a type III. Both of these cases showed definite electrocardiographic changes. Case 29, who had a probable syphilitic nephrosis, showed low amplitude T waves in all leads. These changes, however, were not sufficiently abnormal to be included in the 15 cases showing changes. Case 12 had x-ray and physical evidence of a periostitis, and an initial blood test of 512 Kline units. There were, however, no cardiac changes. No case of ocular or liver involvement was noted in this series.

Controls.—Eight patients showing no historical, physical, or serologic evidence of syphilis were treated with the same amounts of penicillin as the thirty syphilitic patients. These control cases had minor dermatologic diseases such as pyodermas, and so forth, with no evidence of systemic disease. None of these eight showed any electrocardiographic changes during or after the administration of 4.8 million units. This control series is admittedly small. In view of the fact that the majority of the electrocardiographic changes in the syphilitic patients were seen prior to the administration of penicillin, we think this control significant.

CASE REPORTS

CASE 11.—A 29-year-old white man was admitted to the Institute for the Study of Venereal Disease of the Hospital of the University of Pennsylvania on June 12, 1946, with the diagnosis of seronegative primary syphilis.

The patient, a merchant seaman, landed in this country June 3, 1946. His last sexual contact was in India some four weeks before, just prior to embarking for the United States. He gave a blood transfusion to a friend the day he landed, and a confirmed blood test on June 3 was negative. On June 4, he noted a small papule near the fernulum. This progressed to an ulcer 1 cm. in diameter by June 11. He had taken no digitalis or other drugs.

The patient was 5 feet, 8½ inches in height and weighed 136 pounds. The blood pressure was 126/80, the oral temperature was 98.6° F., and the pulse 80 per minute. There was a sharply defined ulcer on the glans penis extending to the frenulum and a 1 cm. x 1.5 cm. nonpainful node in the left inguinal region. No other skin or mucous membrane lesions were present. Examination of the heart showed no enlargement, no murmurs, and a regular rhythm. The electrocardiograms are shown in Fig. 4.

The important laboratory data include: a positive dark-field examination of material from penile lesion on June 11, 1946; negative Kline, Kolmer, Mazzini, and Kahn tests on June 11, 1946; negative Kolmer, Kline, and Mazzini tests again in July, 1946; and a cerebrospinal fluid examination, June 19, 1946, which showed 2 cells, Wassermann 0000, protein 30 mg., and mastic 0000000000.

The patient was started on 80,000 units of sodium penicillin; six hours later he had a chill and then a temperature of 102° F. by mouth. His pulse was 118 per minute at the height of fever, but on the following day when his temperature had fallen to 101°, his pulse was 130. By the third day both pulse and temperature had leveled off and remained normal throughout the hospital stay. He received 120 injections of 80,000 units each between June 12 and June 27, 1946. At no time did he complain of cardiac symptoms.

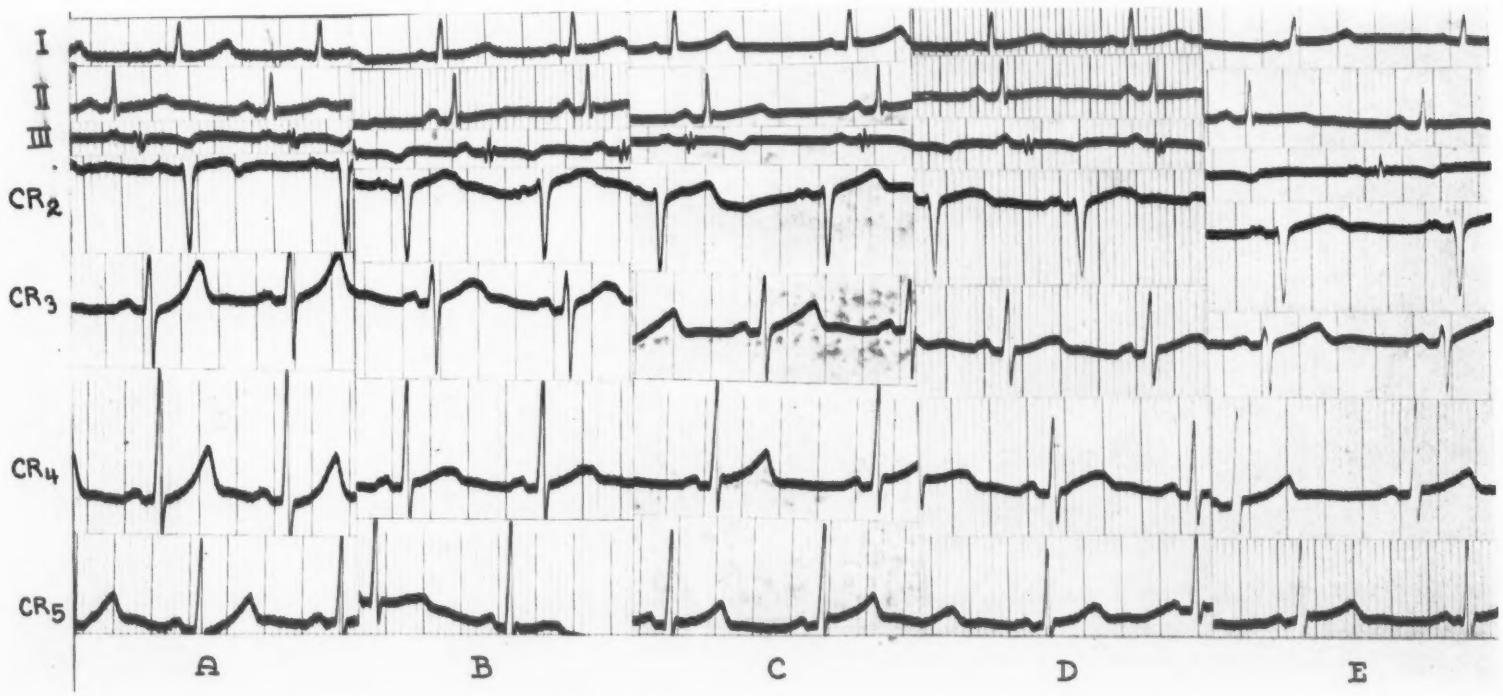


Fig. 5.—Case 3. *A*, Electrocardiogram of young colored girl, 23 years of age, with secondary syphilis, made May 29, 1946, before treatment. *B*, Tracing made on June 8, 1946. Tracings made in the interim were similar to May 29, 1946. *C*, Electrocardiogram made June 11, 1946, and *D*, one month later, July 11, 1946. *E*, Tracing made Sept. 4, 1946. Eight electrocardiograms made between *D* and *E* showed fleeting changes, but tracings made Oct. 1, 1946, and Nov. 6, 1946, were similar to *E*.

CASE 3.—A colored woman, 23 years of age, was admitted to the Institute for the Study of Venereal Disease of the Hospital of the University of Pennsylvania on May 29, 1945, with a diagnosis of secondary syphilis.

The patient had negative serologic tests for syphilis in 1939 and in 1942, and gave no history of previous antisyphilitic treatment. A small lesion on the labia was noted two months before admission. This cleared spontaneously, but one month later numerous lesions appeared over the entire vulva and trunk. There was no history of digitalis or other drug ingestion.

The patient was 5 feet, 2 inches in height and weighed 118 pounds. Her oral temperature was 98° F., respiration, 20, pulse, 72 per minute, and blood pressure, 118/70. There were resolving hyperpigmented papules over the trunk, macules of the palms and soles, and condylomatous lesions of the genitalia and perineum. The throat was inflamed and her voice was slightly husky. The heart was normal in size and the sounds were of good quality, no murmurs were heard. The electrocardiograms are shown in Fig. 5.

The important laboratory data were as follows: dark field from condylomata positive for *Treponema pallidum* on May 29, 1946; Kolmer positive, Mazzini positive, Kline 256 units on May 29, 1946; a cerebrospinal fluid examination on June 5, 1946, showed 1 cell, Wassermann 0000, protein 10 mg., and mastic 0000000000.

The patient received the first injection of 80,000 units of sodium penicillin on May 29, 1946, and this was continued every three hours for 120 injections. She completed the 9.6 million units on June 18, 1946, without nausea, cardiac symptoms, urinary difficulties, or pain. There was no Herxheimer reaction as far as temperature, pulse, or skin were concerned.

CASE 14.—A 47-year-old colored man was admitted to the medical ward of the Hospital of the University of Pennsylvania on July 24, 1946, for observation of abdominal pain and vomiting of four weeks' duration. A penile lesion of approximately six weeks' duration was discovered along with a follicular eruption of approximately three weeks' duration. There was a history of annual negative blood tests since 1940.

On physical examination he was 5 feet, 8½ inches in height, weighed 126½ pounds, and his oral temperature was 99° Fahrenheit. His respiration was 18, pulse, 82 per minute, and blood pressure, 130/80. The patient was emaciated and vomited frequently. There was a follicular eruption on the arms and macules on the palms and soles. The urethra was indurated and small indurated ulceration could be seen at the meatus. The deep reflexes and pupillary reflexes were normal. There was generalized lymphadenopathy and the liver was enlarged 2 cm. below the costal margin. Roentgen study of the gastrointestinal tract disclosed gastric retention with spasm and deformity of the antrum. A gastroscopy performed Aug. 6, 1946, disclosed an ulcer of pyloric antrum with scarring of lesser curvature. The cardiac findings were negative and there was no history of digitalis or other drug ingestion. The electrocardiograms are shown in Fig. 4.

The important laboratory data were as follows: dark field from meatus positive for *Treponema pallidum* on July 31, 1946; Kolmer and Mazzini strongly positive, Kline 256 units on July 31, 1946; and a cerebrospinal fluid examination on July 29, 1946, which showed no cells, Wassermann slightly positive, protein 60 mg., and colloidal gold 0111000000.

The patient was started on 40,000 units of sodium penicillin on July 31, 1946. There was no febrile or clinical Herxheimer reaction. Thirty-six hours after the start of the penicillin, however, all nausea and vomiting ceased and the course was uneventful. Because of the gastric lesion in a man of 47 years, he was operated upon and the nonspecific ulcer was found. He did not complain of cardiac symptoms before or after operation.

CASE 19.—A 37-year-old white man entered the Institute for the Study of Venereal Disease of the Hospital of the University of Pennsylvania on April 15, 1946, as contact of his bride of three months, who had florid secondary syphilis. He was clinically and serologically negative at the time, but returned two weeks later, May 2, 1946, with a large, indurated, dark-field positive penile lesion. There was no history of digitalis or other drug ingestion.

The patient was 5 feet, 8 inches in height, and weighed 151 pounds. His temperature was 98.2° F., his pulse, 72 per minute, and blood pressure, 122/78.

On his first admission, May 2 to May 19, 1946, there was an indurated ulcer on the corona, satellite lymphadenopathy in the right inguinal region, but no generalized lymph node enlarge-

ment. There were no other skin or mucous membrane lesions. Examination of the cardiovascular system was entirely normal except for the electrocardiogram; he had no cardiac complaints. The electrocardiograms are shown in Fig. 2.

The important laboratory data were as follows: Dark-field positive penile lesion on May 2, 1946; Kolmer and Eagle strongly positive, and Kline 64 units on May 2, 1946; and a cerebral spinal fluid examination on May 8, 1946, which showed 1 cell, Wassermann 0000, protein 20 mg., and mastic 0000000000.

The patient was started on 80,000 units of sodium penicillin on May 4, 1946, and received 120 such injections intramuscularly at three-hour intervals (total, 9.6 million units). The lesion was completely healed and all induration gone on June 21, 1946. Blood tests showed: Kolmer strongly positive, Kline 64 units on June 3, 1946; and Kolmer doubtful, Kline less than one unit on June 21, 1946.

His second admission was from July 31 to Aug. 15, 1946. A lesion had appeared one week before at the same site as the previous one. There were solitary nodes in the right inguinal region, but no other skin or mucous membrane lesions were present. Examination of the heart revealed no changes compared to May 19, 1946, except that the electrocardiogram was normal.

The important laboratory data were as follows: dark field from penile lesion positive for *Treponema pallidum* on July 31, 1946; Kolmer strongly positive, Kline 256 units on July 31, 1946; and a cerebral spinal fluid examination on Aug. 2, 1946, which showed 1 cell, Wassermann 0000, protein 20 mg., and mastic 0000000000.

The patient was started on 80,000 units of sodium penicillin on July 31, 1946, and received 120 injections at three-hour intervals for a total of 9.6 million units. Again the lesion completely epithelialized by the end of treatment. He had a moderate postspinal headache which disappeared in forty-eight hours. On the thirteenth hospital day, he developed typical giant urticaria which was relieved by Benadryl. The penicillin therapy was not interrupted. The patient was seen on Sept. 12, 1946, at which time he showed no clinical evidence of syphilis, his chancre site being nonindurated, Kolmer positive, and Kline 32 units.

His third admission was from Oct. 4, 1946, to Oct. 20, 1946. The lesions reappeared eight days before admission (Sept. 26, 1946) at the same site as the previous ones, and had the same general configuration as the previous ones. General examination was essentially negative except for two discrete lymph nodes in the right inguinal region. Examination of the heart showed no changes compared to Aug. 31, 1946; the electrocardiogram was normal.

Important laboratory data were as follows: Darkfield from penile lesion was positive for *Treponema pallidum* on Oct. 4, 1946; Kolmer and Mazzini were strongly positive, Kline 256 units on Oct. 4, 1946; and a cerebral spinal fluid examination on Oct. 9, 1946, showing 1 cell, Wassermann 0000, protein 10 mg., and mastic 0000000000.

The patient was started on sodium penicillin, 80,000 units every three hours for 120 doses. No febrile or clinical Herxheimer reaction was present and no evidence of urticaria or pruritus was noted.

This patient's only admitted contact, his wife, was followed during this siege of relapses and had been seropositive without lesions until Oct. 6, 1946, when she developed dark-field positive secondaries and was admitted for study.

DISCUSSION

It is well known that factors other than actual heart disease, such as drugs, change in position from recumbent to sitting or standing, autonomic nerve influences, and changes in the constitution of the blood, for example, hyperventilation, may produce changes in the T waves of the electrocardiogram. Even trivial influences such as smoking, or drinking cold liquids, or even mild exertion may also cause changes in the T waves. To the best of our knowledge, however, these factors were not operative on our cases. Studies of large series of normal young individuals have shown T-wave and RS-T segment changes to occur in a

small percentage of cases. In Ferguson and O'Connell's[14] series of 1,812 midshipman who were clinically normal, eight showed T waves in Lead II which were negative, isoelectric, or diphasic; but in no case was the T wave in Lead I negative or diphasic. In 299 unselected college students, of whom 295 were clinically negative, studied by Wood, Wolferth, and Miller,[15] elevation of the RS-T segment was noted in eighteen and the T wave in Lead II was partly inverted in four, but in no case was the T wave in Lead I inverted. In sixteen instances, however, the height of the T wave in Leads I and II or both, was 1 mm. or less. In Graybiel, McFarland, Gates, and Webster's[16] series of 1000 young men, the RS-T segment was occasionally elevated more than 1 mm., but was rarely displaced downward. The T wave in Lead II was inverted in two instances, and in one case it was diphasic; in Lead I, the T wave was sometimes low, but in no instance was it inverted. These studies emphasize that RS-T segment and T-wave changes occur in supposedly normal young individuals, but also emphasize their rarity. In the older age groups, Wood, Wolferth, and Miller[15] studied 229 corporation executives, a large majority of whom were older than 40 years. In this group abnormal electrocardiograms were found in sixteen and questionable findings were present in 107 others. In the former, however, which included T waves inverted or partly inverted in Leads I and II, all had cardiovascular disease or were known to have suffered from it subsequently, except two who were not followed. It follows, therefore, that while the T wave in Lead II may occasionally be inverted or diphasic in the electrocardiogram of supposedly normal individuals, an inverted or diphasic T wave in Lead I is rarely observed except in the presence of a cardiovascular abnormality.

In all our cases, electrocardiograms were made at frequent intervals, and although too much importance might not be attached to certain changes in the T wave or RS-T segment in individual tracings, the fact that they varied in different electrocardiograms of the same individual taken at frequent intervals, and sometimes in different leads, would indicate that the changes were significant. Slight changes in the amplitude of T waves were not considered significant and these cases are not included in the abnormal group. In one case (Fig. 2.), however, the initial electrocardiogram was considered doubtful, but the gradual improvement in the T waves over a period of eleven days while under treatment indicated that the slight T-wave changes were abnormal for this individual. Although none of the 3,107 subjects included in the three large groups of supposedly normal young individuals showed inversion of the T wave in Lead I, three (20 per cent) of the fifteen cases considered abnormal in this study showed inverted T waves in Lead I in at least one of the electrocardiograms. Furthermore, the large percentage of patients (50 per cent) who showed changes in the electrocardiogram, either before or during treatment, suggests that the abnormalities observed in the electrocardiogram could not be due to extracardiac factors, although in no instance were there any complaints referable to the cardiovascular system. In the absence of autopsy material and because there is such marked difference of opinion (Boyd,[5] and Warthin[9]) as to changes which occur in the heart muscle in early syphilis, one can only spec-

ulate as to the possible causes of the electrocardiographic abnormalities. Several possibilities present themselves:

1. That they are due to a toxic action of penicillin, such as that which has been attributed to arsenic, sulfonamides, and other drugs.

2. That the changes are due to a toxemia without actual cardiac involvement, such as occurs in some infectious diseases.

3. That the abnormalities are due to a distrubance in the heart muscle either because of direct action of the spirochetes within the heart muscle or intercellular spaces or by their destruction by penicillin.

We believe the first possibility can be dismissed because: (1) In eleven cases T-wave or RS-T segment changes were present before treatment with penicillin or before other forms of treatment were initiated. (2) In our experience comparable changes were not present in penicillin-treated infections due to other causes. (3) In a small control series, eight subjects, there was no instance of electrocardiographic change while penicillin was being used. Although small, this control group is considered significant since the majority of changes that developed in the abnormal group occurred before treatment.

The suggestion that the electrocardiographic changes may be of toxic origin seems to be refuted by the fact that there was no clinical, urinary, or hematologic evidence of toxemia except during a short period (usually six to twelve hours after treatment was started) when a sharp rise in temperature of Herxheimer type occurred in one-third of the cases. However, in most cases the electrocardiograms showed changes while the patient was apparently well and after treatment was completed, and there was no correlation between Herxheimer reactions and electrocardiographic changes. Young[17] recently reported thirteen cases with electrocardiographic changes as the result of upper respiratory infections. As in our cases, changes frequently occurred while the patient was apparently well, but he states that in the few cases reported in the literature where sudden death occurred during acute tonsillitis, a diffuse widespread myocarditis was found at autopsy. In the absence of autopsy material, however, one cannot state categorically that the changes in our group of cases are not of toxic origin.

In our opinion the possibility that the electrocardiographic abnormalities are due to changes within the heart muscle seems most tenable. As stated previously, however, the lack of autopsy material and the marked difference in the opinion of pathologists as to the cardiac changes in early syphilis, makes this suggestion a very fertile field for speculation.

CONCLUSIONS

1. Thirty cases of early infectious syphilis were studied and fifteen showed definite electrocardiographic changes, but in no instance were there cardiac complaints.

2. The electrocardiographic abnormalities consist of T-wave and RS-T segment changes in limb and/or chest leads.

3. There is no correlation between the febrile Herxheimer reaction and the incidence of these electrocardiographic changes.

4. The electrocardiographic abnormalities occur in all stages of early infectious syphilis.

5. Penicillin does not appear to be responsible for these electrocardiographic changes.

6. In some instances the changes are transient, but in others they may last for several months; it is not possible to state at this time whether the changes may be permanent.

Special acknowledgment is made of the valuable aid of Charles C. Wolferth, M.D., Director of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, whose departmental facilities and direction were made available for this work; and of the helpful suggestions and criticisms of Dr. John H. Stokes.

REFERENCES

1. Arnett, J. H.: Cardiovascular Findings in Women With Syphilis, Am. J. M. Sc. **176**:65, 1928.
2. Wilson, F. W., Wile, W. J., Wishart, S. W., and Herrmann, G. R.: Changes in the EKG Following Arsphenamine Treatment of Cardiac and Aortic Syphilis, Proc. Soc. Exper. Biol. & Med. **23**:275, 1926.
3. Chamberlain, E. W., and Follows, J. H.: The EKG in Syphilis. An Examination of 232 Cases of Syphilis and 156 Controls, Quart. J. Med. **26**:221, 1933.
4. Martland, H. S.: Syphilis of the Aorta and Heart, Am. Heart J. **6**:1, 1930.
5. Boyd, W.: A Text-Book of Pathology: An Introduction to Medicine, Philadelphia, 1943, Lea & Febiger, p. 365.
6. Turner, K. B., and White, P. D.: The Heart and the Aorta in Early Syphilis, Arch. Int. Med. **39**:1, 1927.
7. Grassmann, K.: Klinische Untersuchungen an den Kreislaufs-organen in Frühstadium der Syphilis, Deutsches Arch. f. klin. Med. **68**:455, 1900.
8. Warthin, A. S.: Primary Tissue Lesions of the Heart Produced by Spirochaeta Pallida; Trans. XVII, Internat. Congress Med., Sec. Path. Part II, 299, 1913.
9. Ibid: Primary Tissue Lesions in the Heart Produced by Spirochete Pallida, Am. J. M. Sc. **140**:7, 1914.
10. Sadusk, J. F.: Discussion of Papers by Leifer, Chargin, and Hyman, and Elliott, Baer, Shaffer, Usher, and Lough, J. A. M. A. **117**:1165, 1941.
11. Geiger, A. J., Craig, B., and Sadusk, J. F.: Observations in the Massive Dose Arsenotherapy of Early Syphilis by the Drip Method II. Electrocardiographic Abnormalities Associated With Massive Arsenotherapy, Yale J. Biol. & Med. **14**:357, 1942.
12. Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology, Philadelphia, 1945, W. B. Saunders Company.
13. Klotz, S. D., and Crede, R. H.: Electrocardiographic Changes in Early Syphilis Prior to and Upon Completion of Intensive Arsenotherapy, Am. Heart J. **30**:551, 1945.
14. Ferguson, D., and O'Connell, J. T.: Cardiovascular Observations, U. S. Nav. M. Bull. **24**:860, 1926.
15. Wood, F. C., Wolferth, C. C., and Miller, T. G.: Electrocardiography in War Medicine, War Med. **1**:696, 1941.
16. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analsyis of the Electrocardiograms Obtained From 1000 Young Healthy Aviators, Am. Heart J. **27**:524, 1944.
17. Young, D.: Electrocardiographic Changes Occurring During Upper Respiratory Infections, Am. Heart J. **32**:303, 1946.

COMPARATIVE STUDY OF POTASSIUM THIOCYANATE AND OTHER DRUGS IN THE TREATMENT OF ESSENTIAL HYPERTENSION

ARTHUR RUSKIN, M.D., AND W. FRANK MCKINLEY, M.D.*
GALVESTON, TEXAS

HUNDREDS of drugs have been and are being used in the therapy of essential hypertension, frequently without critical analysis of their value in either abolishing symptoms or lowering the systolic and diastolic blood pressure. Ayman[1,2] has pointed out the enormous variabilities of blood pressure under various conditions with or without therapy. He noted variations in systolic pressure up to 40 to 100 mm. of mercury. Every practitioner has seen hypertension of over 220/120 interspersed with long periods of normal blood pressure without therapy of any kind. Claims of symptomatic relief from headaches, dizziness, and other symptoms of essential hypertension by various methods of therapy have been countered by noted relief from symptoms in 82 per cent of the cases following administration of dilute hydrochloric acid in placebo dosage.[3]

More recently, Kapernick[4] studied the effect of several reputedly hypotensive drugs, including xanthine derivatives, phenobarbital, erythrol tetranitrate, and representatives of the mistletoe and garlic groups, with negative results. However, the various drugs were tried in different small groups of cases, and potassium thiocyanate was not among them. In the comparative study of Evans and Loughnan[5] numerous therapeutic methods, including potassium thiocyanate, were tested in similar fashion and found wanting. In general, symptomatic relief was as common, and significant drops in blood pressure as infrequent, in the placebo as in the other groups. Potassium thiocyanate apparently caused actual increases in symptoms and blood pressure in a minority of cases.

Since the introduction of blood level checks in thiocyanate therapy by Barker[6] in 1936, twenty-one favorable and five unfavorable reports on its efficacy in human hypertension have been listed.[7] The same reviewer stated, however, that "none of the clinical reports have completely eliminated all the variables which might cause unrelated blood pressure variation." Barker and associates[8] have now treated some hundreds of patients for years, with favorable effects in some half to three-quarters of their cases. Their criteria of falls of systolic pressure, 30 to 60 mm., and of diastolic 20 to 40 mm., would seem adequate except for lack of adequate controls and questionable methods of measuring the changes in blood pressure, as critized later in this discussion. Provided

*From the University of Texas Medical School, and the Heart Station of the John Sealy Hospital, Galveston.

Received for publication Feb. 24, 1947.

the blood level of potassium thiocyanate was kept at 8 to 12 mg. per cent, serious or fatal toxic reactions were avoided.

Nevertheless, the Council of Therapy of the American Medical Association has failed to endorse this mode of therapy on the grounds of incomplete proof of its efficacy in human essential hypertension, its toxic effects, and its failure to lower the blood pressure in experimental hypertensive animals except at toxic blood levels.[9] The pharmacologic mode of action of the thiocyanates is also far from clear, although numerous theories have been proposed.[7] While one group of investigators[10] has claimed that normal (pretreatment) serum thiocyanate is inversely proportional to the blood pressure, thereby providing a rational support for its therapeutic use in hypertension, others[11] have been unable to confirm this.

A restudy of the preceding claims, with adequate controls, was begun by us in 1942. Since then, six drugs, unknown to the patients, have been administered in various rotations to sixty-eight clinic patients with uncomplicated essential hypertension. The dosages were as follows: phenobarbital, 32.0 mg. three times daily; glucophylline (methyl-xanthine derivative), 0.3 Gm. three times daily; mannitol hexanitrate, 65.0 mg. three times daily; niacin, 50.0 mg. three times daily; and a placebo (lactose or sodium bicarbonate), 0.3 Gm. three times daily. Periods of therapy were interspersed with rest or control intervals of two to four weeks. Potassium thiocyanate was started at 0.2 Gm. three times a day after three blood serum levels were obtained in the fasting state and following a tobacco-free interval of three or more days, as recommended.[11] Serum potassium thiocyanate concentration was determined by a method adapted to the Evelyn colorimeter.[12] In many cases, weekly blood levels reached 20 mg. per cent (to evaluate the drug more thoroughly), and, at times, inadvertently, higher levels. Maintenance dosages of potassium thiocyanate necessary to maintain therapeutic blood levels varied from 0.2 to 1.2 Gm. daily, and the drug was continued for three months, as recommended for proper evaluation.[8] The rest interval after thiocyanate therapy was at least a month, or long enough for return to the pretreatment blood level.

Blood pressures were recorded twice weekly between 9 and 10 A.M., in the same arm, by the same observer, and to the nearest 5 mm. of three readings, recording both the fourth and the fifth phases whenever possible.[13] Constant conditions of preliminary rest and medication were observed.

RESULTS

It was found that two kinds of estimates of the effect of the various drugs upon the blood pressure checked closely and disagreed markedly with the usual method of contrasting the blood pressure just before and following the therapeutic agent. One was to compare the range of systolic and diastolic pressures during the control and therapeutic periods. The other was to contrast the medians of the numerous blood pressure readings during medicinal and drugless periods. When, as happened infrequently, the two computations disagreed by 5 mm., the figure closer to the one obtained by the before-and-after method was

taken as the correct result. It cannot be too strongly emphasized, however, that results obtained from the graphed blood pressures before and during drug administration (Fig. 2), depending as they do upon the fallacy of taking a variable (the pretreatment blood pressure) for a constant, are probably worthless, even for comparative purposes.

The weighted results of the effects of the six drugs upon the systolic and diastolic blood pressures are charted in Fig. 1 and Table I. It will be seen that while potassium thiocyanate was associated, especially in isolated instances, with more marked drops in systolic and in diastolic pressures than the other

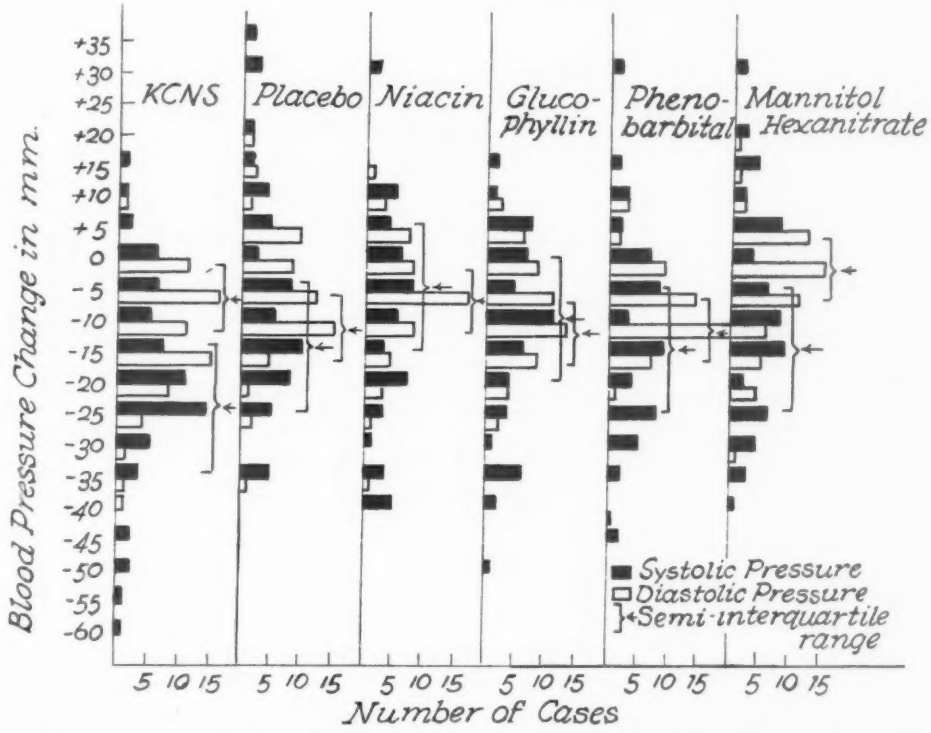


Fig. 1.—Effects of the six drugs upon the systolic and diastolic blood pressures, as finally obtained from range-to-range and median-to-median comparisons of the control and therapeutic periods. Minus signs indicate falls; plus signs, rises in pressure.

drugs, tremendous overlapping was present. Mild to moderate drops in blood pressure were frequent following the exhibition of all six drugs, as had been noted previously with and even without various modes of therapy.[2] In a small minority, no changes and even actual rises in blood pressure occurred during thiocyanate therapy. This undoubtedly occurred more frequently following the use of the other drugs.

Statistical analysis, for which we are indebted to Dr. J. A. Scott,* revealed somewhat unexpected differences between the results of administration of po-

*Professor of Epidemiology and Statistics.

tassium thiocyanate and the other drugs. The critical ratio of the difference between the means of potassium thiocyanate and placebo in regard to their effects upon the systolic blood pressure was 3.6, and diastolic pressure, 3.5; or the probability of the correctness of the assumption that there was no difference in the two series of results, or that it was due to chance, was less than one in one thousand. On the other hand, the critical ratio of glucophylline and placebo, for example, was 1.3 for the systolic and 1.16 for the diastolic pressure results; or a probability of chance differences of forty in one hundred.

TABLE I. FIGURES OF AVERAGE AND MEDIAN FALLS IN PRESSURE FOLLOWING THE SIX DRUGS, OBTAINED AS DESCRIBED IN FIG. 1 AND IN TEXT

	LOWERING OF BLOOD PRESSURE BY VARIOUS DRUGS			
	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
	AVERAGE	MEDIAN	AVERAGE	MEDIAN
1. Potassium thiocyanate	19.5 mm.	25 ± 10 mm.*	10.6 mm.	5 ± 5 mm.
2. Placebo	9.4	15 ± 10	5.4	10 ± 5
3. Niacin	11.1	5 ± 10	4.9	5 ± 5
4. Glucophyllin	12.8	10 ± 10	7.0	10 ± 5
5. Phenobarbital	12.8	15 ± 10	7.1	10 ± 5
6. Mannitol hexanitrate	8.1	15 ± 10	3.8	0 ± 5

*Semi-interquartile range.

A more familiar graphing of results of thiocyanate therapy is seen in Fig. 2, which demonstrates the generally more marked effect of potassium thiocyanate in lowering the systolic rather than the diastolic blood pressure. Fig. 2 also shows that there is no consistent relation between the levels of potassium thiocyanate and the blood pressures during therapy. Nevertheless, in those patients in whom serum thiocyanate exceeded 15 mg. per cent, diastolic pressures fell over 10 mm. twice as often as they failed to be lowered; whereas, in those with serum levels below 15 mg. per cent, diastolic pressure depressions failed to occur in the majority of cases (Table II).

TABLE II. BLOOD PRESSURE DEPRESSION AND THERAPEUTIC SERUM POTASSIUM THIOCYANATE LEVEL IN SIXTY-EIGHT CASES

SERUM POTASSIUM THIOCYANATE	S. P. FALL 20 MM. PLUS	S. P. FALL <20 MM.	D. P. FALL 10 MM. PLUS	D. P. FALL <10 MM.
Over 15 mg. per cent	26	15	27	14
Under 15 mg. per cent	17	10	11	16

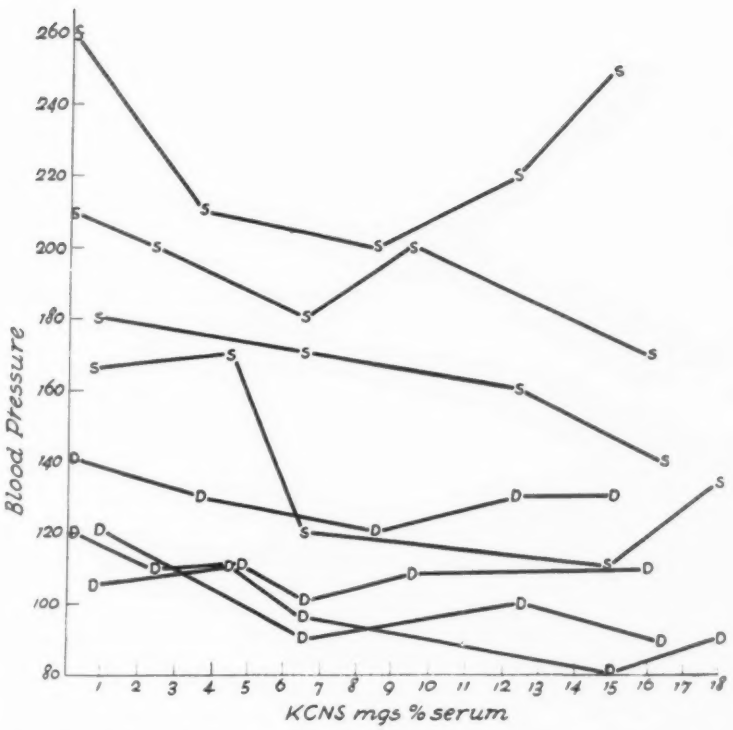


Fig. 2.—Serial systolic and diastolic blood pressures in four representative cases treated with potassium thiocyanate, graphed with regard to the level of serum thiocyanate, but not all in temporal sequence.

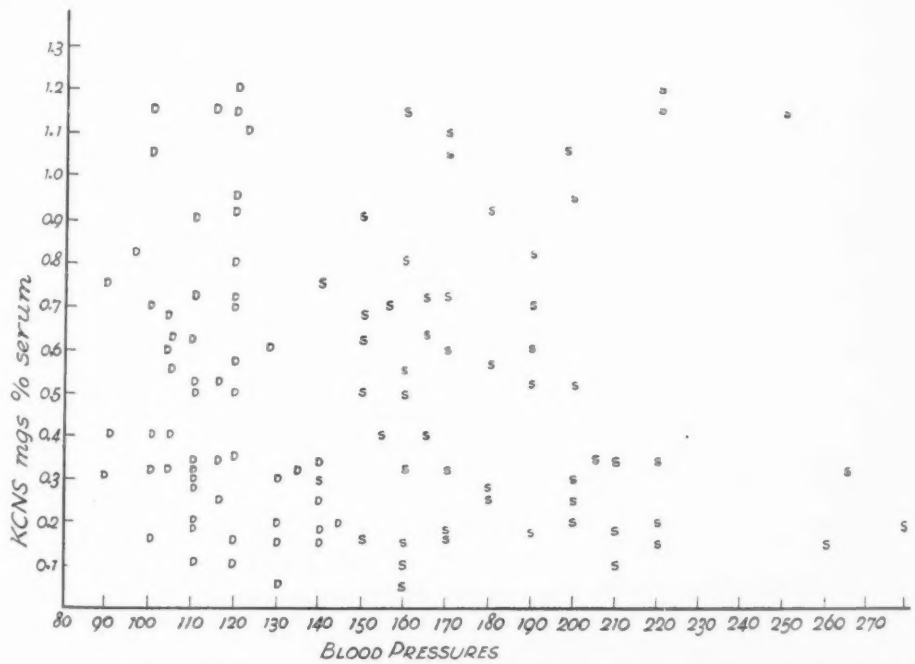


Fig. 3.—Average fasting serum levels of thiocyanate or thiocyanate-like substance obtained after a tobacco-free interval and before potassium thiocyanate therapy, plotted against the systolic (S) and diastolic (D) blood pressures of the same hypertensive patients.

A general lack of correlation between the systolic and diastolic blood pressures of hypertensive patients and the resting levels of serum thiocyanate is seen in Fig. 3. This contradicts the results of Caviness and associates.[10] A similar lack of correlation is demonstrable for normotensive individuals (fifty cases, not shown). It is to be admitted that the method is inexact for such small amounts of thiocyanate or thiocyanate-like substance as are present in normal and hypertensive sera. While the resting serum levels varied from 0 to 1.93 mg. per cent, variations up to 50 per cent in successive determinations in the same individuals were not uncommon, particularly for very low levels.

Relief of symptoms was greatest in the groups receiving the placebo and niacin, and least in the group receiving potassium thiocyanate (Table III). The incidence of actual increase in symptoms was about equal in all groups except the group receiving thiocyanate, which presented the most marked additional complaints. Not unexpected were the occasional dizziness in the hexanitrate-treated patients, and sleepiness or loss of libido in the phenobarbital-treated group. The presumable toxic effects of potassium thiocyanate are listed in Table IV. The most common were dizziness, fatigability and weakness, headache, and nausea. In cases in which serum thiocyanate reached over 15 mg. per cent, symptoms occurred or were intensified in thirty of forty-two cases; in those in which serum thiocyanate remained below 15 mg. per cent, symptoms occurred or were intensified in only thirteen of twenty-six cases.

TABLE III. EFFECTS OF VARIOUS DRUGS ON SYMPTOMS IN SIXTY-EIGHT HYPERTENSIVE PATIENTS

	INCREASE	SAME	DECREASE
Potassium thiocyanate	32	17	19
Placebo	12	5	51
Niacin	12	8	48
Glycophylline	15	10	38
Phenobarbital	15	16	37
Mannitol hexanitrate	20	11	37

TABLE IV. POSSIBLE TOXIC EFFECTS OF POTASSIUM THIOCYANATE IN SIXTY-EIGHT HYPERTENSIVE PATIENTS

Dizziness	26	Blurred vision	2
Weakness	19	Tinnitus	2
Headache	17	Psychosis	2
Nausea	15	Anorexia	2
Malaise, aches	9	Vomiting	2
Nervousness	8	Pruritus	2
Dyspnea	7	Urticaria	2
Palpitation	7	Edema of face	2
Precordial pain	7	Thyroid enlargement	2
Epigastric distress	7	Conjunctivitis	1
Gaseous distention	5	Polyphagia	1
Sleepiness	5	Paresthesias	1
Insomnia	3	Petechial rash	1
Syncope	3	Maculopapular rash	1

In one case, the drug had to be discontinued because of a generalized scaling papular rash, with a serum thiocyanate level of only 4.3 mg. per cent. In another, a psychotic state preceded by a few weeks a rather acute onset of fatal uremia, left ventricular failure, and lobar pneumonia in a 65-year-old Negro, with serum thiocyanate reaching 21.4 mg. per cent before discontinuance of the drug at the appearance of confusion. A 69-year-old Negro also developed a mild psychosis at a thiocyanate serum level of only 12.6 mg. per cent, when the drug was discontinued. Neither of these patients presented any signs of serious renal damage at the time of onset of thiocyanate therapy; maximum specific gravities were 1.018 and 1.022, and urea clearances 64 and 78 per cent of normal, respectively. On the other hand, two patients, receiving 0.2 Gm. of potassium thiocyanate three times daily, developed temporary blood serum levels over 25 mg. per cent without symptoms of any sort.

Hematologic studies under the direction of Dr. W. C. Levin yielded negative results concerning the effects of potassium thiocyanate upon the blood platelets, bleeding and coagulation times, prothrombin time, and rapidity and completeness of clot retraction. Further investigation is needed for explanation of the reported complication of potassium thiocyanate therapy, thrombophlebitis,[14] which we did not find in our series. Occasional slight anemia resulted from prolonged thiocyanate therapy. Serial electrocardiograms, venous pressures, and circulation times (thiamine) showed no significant changes. Preliminary studies also have failed to reveal marked changes in serial inulin or diodrast renal clearances in our patients treated with potassium thiocyanate.

COMMENT

We are faced with a choice between the clinical impression of the apparent general inefficacy of potassium thiocyanate in relieving symptoms or of markedly surpassing the blood pressure-lowering effect of a placebo and other drugs, and the statistical evidence that exhibition of potassium thiocyanate is followed by more than chance lowering of blood pressure in comparison with other drugs. The majority of clinical reports and surveys,[6-8,15-23] though they lack adequate controls, have come to more unequivocal conclusions, namely, that potassium thiocyanate does relieve symptoms, as it drops elevated blood pressure. Thus, Barker and associates,[8] in their extensive experience, have noted hypotensive as well as favorable symptomatic effects of potassium thiocyanate in 47.5 per cent of cases, purely hypotensive effects in an additional 19.5 per cent, and symptomatic relief in 9 per cent more. In fairness to these investigators it should be pointed out that our serum thiocyanate values rose higher than the recommended ones of 8 to 12 or 5 to 15 mg. per cent. Yet complaints were present or increased in one-half of our thiocyanate-treated patients with serum values below 15 mg. per cent. The differentiation of hypertensive or neurotic symptoms from toxic effects of potassium thiocyanate is admittedly very difficult. Comparisons are possible in our study, however, with the more favorable symptomatic effects of the other drugs.

In view of the reported lowering of blood pressure by 30 to 60 mm. for long periods by two Russian investigators,[24] following six to eight injections of distilled water, such claims as successful hypotensive and symptomatic results in one-half of a group of selected hypertensives from intramuscular injections of pitressin tannate in oil[25] must be viewed with scepticism. Most reports of various modes of therapy similarly claim improvement in approximately one-half of the patients.

The possible hypotensive effects of the various drugs are to be interpreted also in the light of the conduct of our study. It is undeniably true, as in the case of hypnotic doses of oral and intravenous barbiturates[23] and the usual doses of various nitrites,[25] that the immediate effect of single or consecutive doses of some drugs is definitely hypotensive. We have made no effort to measure the immediate effects of the six drugs except by taking the blood pressures approximately two hours after their administration in the morning. We measured what may be called the average effect of their prolonged administration. This has the virtue of practicality in judging their efficacy in the management of essential hypertension in the clinic, but the disadvantages of possibly missing their temporary hypotensive effect.

With these reservations, we may conclude that some degree of lowering of blood pressure generally followed the exhibition of all six drugs; that differences in hypotensive effect were difficult to judge clinically, but statistically favored potassium thiocyanate administration; that the diastolic hypotensive effects of potassium thiocyanate were, at least in part, dependent on its high serum levels with their attendant toxic effects.

It is impossible to state with finality from our figures that the toxic effects of potassium thiocyanate, presumably on the cardiovascular as well as other systems, are responsible for its hypotensive effects. Such characterizations have been made for thiocyanate action in human[27] as well as animal subjects.[9] The dangers of severe toxicity, even at low serum levels[25] due in part to marked variations in urinary output,[8,14] have also been emphasized. The actual mode of pharmacologic action of potassium thiocyanate is far from clear. The finding of depression of liver oxidation[15] needs further elucidation. Studies of its effect upon the cardiac metabolism and cardiac output, blood volume, and blood vascular system are in order. The demonstration of occasional increase in cutaneous lymphatic flow[16] may indicate relaxation of arteriolar spasm, but more direct evidences of vasodilation are lacking. No increases in skin temperatures or oscillometric arterial pulsations occurred after the administration of potassium thiocyanate, nor did orthostatic hypotension or carotid sinus hypersensitivity develop, even in the two cases presenting syncopal attacks.[29] Preliminary studies also show negative effects of potassium thiocyanate upon the renal clearances of human hypertensives at therapeutic blood levels.[29] In view of the occurrence of diuresis at toxic levels,[8] animal studies of renal clearances as affected by toxic doses of potassium thiocyanate are in order. In this connection, work in progress in our Department of Pharmacology[30] suggests a depressive influence of potassium thiocyanate in some of our hypertensive patients on the blood potassium level, at least upon its initial administration (Table V).

TABLE V. EFFECT OF LARGE DOSES OF POTASSIUM THIOCYANATE UPON THE SERUM POTASSIUM IN A HYPERTENSIVE PATIENT. MARKED FALL OF POTASSIUM UPON INITIAL ADMINISTRATION, NO DEPRESSION UPON SUBSEQUENT USE OF POTASSIUM THIOCYANATE. (E. A. C., WHITE FEMALE, AGED FORTY-SEVEN YEARS)

DATE	BLOOD PRESSURE	℞	POTASSIUM THIOCYANATE LEVEL MG. PER CENT	K/LEVEL MG. PER CENT
8/27/46	250/130	None	0	21.85
9/16/46	180/110	0.8 Gm. Potassium thiocyanate Q. D.	34.4 (Toxic)	12.2
9/23/46	200/100	Off Potassium thiocyanate 7 days	15.0	14.0
10/11/46	220/115	Off Potassium thiocyanate 17 days	5.02	23.5
10/17/46	190/110	Off Potassium thiocyanate 23 days	0.8 mg.	23.1
11/ 1/46	210/110	Off Potassium thiocyanate 30 days	0.4 mg.	19.2
11/ 8/46	190/105	0.8 Gm. Q. D. 7 days	26.2 mg.	19.7
11/15/46	190/115	Reduced 0.6 Gm. Q. D.	22.4 mg.	21.5
11/21/46	190/120	0.6 Gm. Q. D. 14 days	18.2 mg.	25.2

SUMMARY AND CONCLUSIONS

1. A critically controlled study has been made of the effects of six commonly used types of drugs in human essential hypertension. Potassium thiocyanate was compared, under similar conditions and in the same sixty-eight patients, with five other drugs, including a placebo.

2. The best symptomatic relief was obtained from the administration of a placebo or niacin. Glucophylline, phenobarbital, and mannitol hexanitrate decreased the complaints of fewer patients and increased the symptoms in more cases than the placebo or niacin. Potassium thiocyanate, on the other hand, maintained or increased patients' complaints in almost one-half of the cases, and decreased them in less than one-third. Increase of symptoms undoubtedly occurred more frequently at serum thiocyanate levels above 15 mg. per cent, but was also frequent and, at times, perilous at the more commonly accepted "therapeutic" levels.

3. Hypotensive effects were demonstrable in many cases following the administration of all six drugs, including the placebo. The psychic calming effects of the physician's care and drug administration have been repeatedly emphasized and thus find further corroboration. All drugs, including potassium

thiocyanate, have been followed in some cases by actual rises in blood pressure or no change. Statistically, it has been possible to demonstrate that the thiocyanate period of therapy, when compared with the placebo therapy interval, showed significant drops in systolic and diastolic blood pressures, probably due to thiocyanate administration. Again, the diastolic pressures, at least, fell more markedly at serum levels of potassium thiocyanate above rather than below 15 mg. per cent.

4. Further studies are necessary to elucidate the mode of action of potassium thiocyanate, and to determine with finality whether its hypotensive effects occur at "toxic" or "therapeutic" blood levels. It would seem from our study that its administration is clinically hazardous and unreliable. The occasional marked drop in blood pressure due to potassium thiocyanate may, apart from any toxicity, cause relative cerebral, renal, and myocardial ischemia, and, possibly, other untoward effects in an organism accustomed to a high intra-arterial tension. The role that the inconstant hypotension produced by potassium thiocyanate may play in the prevention of cerebral hemorrhage or of cardiac hypertrophy and failure is not established from present-day data.

5. Clinical reports of the efficacy of drugs and other methods in the treatment of hypertension must be viewed with scepticism, particularly in the absence of control observations.

REFERENCES

1. Ayman, David: Normal Blood Pressure in Essential Hypertension, J. A. M. A. **94**:1214, 1930.
2. Ayman, David: An Evaluation of Therapeutic Results in Essential Hypertension. II. The Interpretation of Blood Pressure Reductions, J. A. M. A. **96**:2091, 1931.
3. Ayman, David: An Evaluation of Therapeutic Results in Essential Hypertension. I. The Interpretation of Symptomatic Relief, J. A. M. A. **95**:246, 1930.
4. Kapernick, John S.: The Blood Pressure in Essential Hypertension: Effect of Several Reputedly Hypotensive Drugs, AM. HEART J. **26**:610, 1943.
5. Evans, W., and Loughnan, O.: The Drug Treatment of Hypertension, Brit. Heart J. **1**:199, 1939.
6. Barker, M. H.: The Blood Cyanates in the Treatment of Hypertension, J. A. M. A. **106**: 762, 1936.
7. Forster, R. E.: The Medical Use of Thiocyanates in the Treatment of Arterial Hypertension, Am. J. M. Sc. **206**:668, 1943.
8. Barker, M. H., Lindberg, H. A., and Wald, M. H.: Further Experiences With Thiocyanates. Clinical and Experimental Observations, J. A. M. A. **117**:1591, 1941.
9. Goldblatt, H., Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension. XVII. Experimental Observations on the Treatment of Hypertension, J. A. M. A. **119**:1192, 1942.
10. Caviness, V. S., Umphlet, T. L., and Royster, C. L.: Blood Pressure and Sulfocyanates (Thiocyanate), Am. J. M. Sc. **204**:688, 1942.
11. Trasoff, A., and Schneeberg, N. G.: The Naturally Occurring Blood Sulfocyanates and Their Relation to Blood Pressure, Am. J. M. Sc. **207**:63, 1944.
12. Elkington, J. R., and Taffel, M.: The Apparent Volume of Distribution of Sulfocyanate and of Sulfanilamide in the Dog, Am. J. Physiol. **138**:126, 1942.
13. Standardization of Blood Pressure Readings. Joint Recommendations, etc., AM. HEART J. **18**:95, 1939.
14. Koffler, A., and Freireich, A.: Thrombophlebitis as a Hitherto Unreported Complication of Thiocyanate Therapy, Am. J. M. Sc. **207**:374, 1944.
15. Robinson, R. W., and O'Hare, J. P.: Further Experiences With Potassium Sulfocyanate Therapy in Hypertension, New England J. Med. **221**:964, 1939.

16. Griffith, J. Q., Jr., Lindauer, M. A., Roberts, Ella, and Rutherford, R. B.: Studies of Criteria for Classification of Arterial Hypertension. VI. Treatment With Thiocyanate, AM. HEART J. **21**:90, 1941.

17. Crockett, K. A., and Moensch, L. G.: Potassium Thiocyanate Treatment of Hypertension, J. A. M. A. **120**:982, 1942.

18. Fanson, E., Kinsey, D., and Palmer, R. S.: Potassium Sulfocyanate Therapy in Essential Hypertension, New England J. Med. **229**:540, 1943.

19. Blumenthal, G. S., and Wetherby, M.: Potassium Thiocyanate in Hypertension, Minnesota Med. **27**:177, 1944.

20. Durant, T. M.: Thiocyanate Therapy in Hypertension, Pennsylvania M. J. **47**:1077, 1944.

21. D'Silva, J. L., and Evans, G.: The Treatment of Arterial Hypertension With Potassium Thiocyanate, Brit. J. Urol. **16**:1, 1944.

22. Ayman, David: Present Day Treatment of Essential Hypertension, M. Clin. North America, **28**:1141, 1944.

23. Page, I. H., and Corcoran, A. C.: Arterial Hypertension, Chicago, 1945, The Year Book Publishers, Inc.

24. Ruskin, A.: A Review of Soviet Cardiology, Am. Rev. Soviet Med. **3**:260, 1946.

25. Griffith, J. Q., Jr., Padis, N., and Anthony, E.: Selection of Patients With Arterial Hypertension for Treatment by Repeated Injections of Pitressin, Am. J. M. Sc. **212**:31, 1946.

26. Weaver, G. C., Willis, J. H., and Hodge, H. C.: Effect on Blood Pressure of Normal Persons and Hypertensive Patients of Glyceryl Trinitrate, Sodium Nitrite, Erythrol Tetranitrate and Mannitol Hexanitrate, AM. HEART J. **28**:601, 1944.

27. Herrmann, George R.: Synopsis of Diseases of the Heart and Arteries, ed. 3, St. Louis, 1944, C. V. Mosby Company.

28. del Solar, A., Dussaillant, G., Brodsky, M., and Rodriquez, G.: Fatal Poisoning From Potassium Thiocyanate Used in Treatment of Hypertension, Arch. Int. Med. **75**: 241, 1945.

29. Ruskin, A., and McKinley, W. F.: Unpublished observations.

30. Emerson, G. A., Ewing, P. L., and Brooks, B. F.: Unpublished observations.

AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

IV. The Effect of Position Change on the Relationships of the Q-T and the T-P Intervals Respectively to the Cycle Length (R-R Interval)

Isadore Schlamowitz, M.D.
New York, N. Y.

HAVING shown that there was a more or less predictable relationship between the Q-T interval and the cycle length, attempts were made to determine the effects of various factors on it. Among these was the effect of change of position. Lombard and Cope[1] studied the effect of position change on this relationship by recording cardiac systole and cycle length by means of mechanical devices. They found that it was disturbed by the shortening of systole out of proportion to the shortening of the cycle length as the position changed from recumbent to sitting. This was still more marked when the standing position was assumed. White and Mudd[2] studied the effect of position change on the ratio of the Q-T interval to the cycle length in the electrocardiograms of five normal subjects. They found that there was a shortening of Q-T and C (cycle length) as the position was changed from supine to sitting and then to standing. However, no disturbance of the ratio was observed. Cheer and Li,[3] in a study of 224 subjects, found that with a change of position from supine to sitting there was a disturbance of the $\frac{Q\text{-}T}{\sqrt{C}}$ ratio. The disturbance consisted of a shortening of the Q-T interval out of proportion to the shortening of the cycle length. Thus, $\frac{Q\text{-}T}{\sqrt{C}}$ became smaller when the position was changed from the supine to sitting. The difference, however, was not statistically significant. White, Kossmann, and Ershler[4] found that $\frac{Q\text{-}T}{\sqrt{C}}$ became smaller when the position was changed from supine to sitting. However, they too found that the difference was not statistically significant. The effect of changing position on the relationship of the T-P interval to the cycle length does not appear to have been reported.

Since there appeared to be disagreement concerning the effect of position change on the Q-T to C relationship, and since the effect of position change on

From the Department of Therapeutics, New York University College of Medicine.
Received for publication Jan. 22, 1947.

the T-P to C relationship had not been reported before, it was decided to investigate these relationships.

METHOD

Fifty-three male medical students who were found to be normal were included in this series. The subject was considered normal only when the history, physical examination, chest fluoroscopy, and exercise tolerance test failed to reveal any evidence of the presence, past or present, of rheumatic fever, cardiac dysfunction, both organic and functional, circulatory disturbances, and other diseases.

The electrocardiograms were taken with a No. 2 Hindle string galvanometer with a string resistance of 2,200 ohms. The instrument was operated at 3 amperes, and the timer was checked and adjusted by means of a stroboscopic arrangement before each tracing was recorded. The timing error was therefore so minute that no corrections were necessary. The three standard limb lead tracings were standardized so that a string deflection of 1 cm. was equivalent to 1 millivolt.

An electrocardiogram was taken of each subject while he was in the supine position. Then, the subject sat up in a comfortable straight-backed arm chair. Another electrocardiogram was taken after he had been seated long enough for the heart rate to become stabilized again. This was necessary because it was found that upon sitting up there was a temporary increase in heart rate. This changing heart rate would have introduced effects that would have invalidated this study. This is more completely discussed in another article.[5]

The criteria for deciding that a tracing was normal and to be used in this study, as well as the method of measuring the Q-T interval, T-P interval, and C, are outlined in previous articles.[6,7] The K(Q-T) for the $\frac{\text{Q-T}}{\text{C}}$ relationship and the K(T-P) for the $\frac{\text{T-P}}{\text{C}}$ relationship for the supine as well as the sitting position were calculated in each case by introdicing the Q-T and T-P and C values into the equations previously determined.[6,7] These are:

$$\text{K(Q-T)} = \frac{\text{Q-T} - 0.167}{\text{C}} \quad \text{and} \quad \text{K(T-P)} = \frac{\text{T-P} + 0.267}{\text{C}}.$$

In Table I is listed the age distribution of the fifty-three subjects retained for this study.

RESULTS

In Table II are listed the K(Q-T) values for both supine and sitting positions for each subject. In order to determine whether there was any significant difference between the two, the means for the K(Q-T) for each position were calculated. It was found that the mean K(Q-T) (supine) was 0.238, with a standard

TABLE I. AGE DISTRIBUTION

AGE (YR.)	NUMBER
19	2
20	5
21	12
22	17
23	12
24	3
25	0
26	1
27	0
28	0
29	0
30	1
Total	53

deviation of ±0.025. The mean K(Q-T) (sitting) was 0.237, with a standard deviation of ±0.021. The difference between the two means was 0.001. Although the difference appears small, it was felt that the *t* value should be determined to help in deciding how significant it was. Even a small difference might be significant, for in the presence of a high correlation between K(Q-T) (supine) and K(Q-T) (sitting) the difference between their means must be very small for it to remain without significance. This determination is briefly outlined as follows:

$$sd = \sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2} - 2r\frac{S_1 S_2}{N}}$$

$$r = \frac{\frac{\Sigma xy}{N} - M_1 M_2}{S_1 S_2}$$

$$r = +0.678$$

$$sd = 0.003$$

$$t = \frac{M_1 - M_2}{sd} = \frac{0.001}{0.003} = 0.333$$

sd = Standard error of the difference between the means.
S_1 = Standard deviation of mean K(Q-T) (supine).
S_2 = Standard deviation of mean K(Q-T) (sitting).
N, N_1, N_2 = Number of cases.
r = Coefficient of correlation between K(Q-T) (supine), K(Q-T) (sitting).
M_1 = Mean K(Q-T) (supine).
M_2 = Mean K(Q-T) (sitting).

Since *t* is so small, the difference between the means is not statistically significant.

In Table III are listed the K(T-P) values for both supine and sitting positions for each subject. In this instance the mean for K(T-P) (supine) was 0.693, with a standard deviation of ±0.030, and the mean for K(T-P) (sitting) was 0.694, with a standard deviation of ±0.027. The difference between the two means here was 0.001. This difference was tested as follows for significance for the reasons outlined previously:

TABLE II. COMPARISON OF THE VALUES FOR K(Q-T) IN THE SITTING AND IN THE RECUMBENT POSITIONS

NO.	CASE	RECUMBENT K(QT)	SITTING K(QT)
1	1002	.224	.230
2	1003	.261	.246
3	1004	.284	.281
4	1005	.208	.190
5	1006	.234	.230
6	1007	.209	.197
7	1008	.294	.267
8	1009	.229	.219
9	1010	.248	.230
10	1011	.220	.219
11	1012	.214	.249
12	1013	.257	.251
13	1014	.265	.262
14	1015	.190	.187
15	1016	.199	.220
16	1017	.258	.285
17	1018	.244	.231
18	1019	.251	.247
19	1020	.225	.221
20	1021	.237	.247
21	1022	.248	.222
22	1023	.228	.250
23	1024	.211	.224
24	1025	.220	.236
25	1026	.225	.233
26	1027	.248	.254
27	1028	.240	.209
28	1029	.251	.233
29	1030	.255	.241
30	1031	.219	.204
31	1032	.248	.256
32	1033	.234	.244
33	1034	.241	.229
34	1035	.282	.270
35	1036	.186	.216
36	1037	.267	.263
37	1038	.248	.245
38	1039	.257	.241
39	1040	.256	.261
40	1041	.224	.235
41	1042	.286	.262
42	1044	.215	.244
43	1045	.223	.247
44	1047	.263	.245
45	1048	.200	.221
46	1049	.220	.250
47	1050	.206	.217
48	1051	.208	.213
49	1052	.223	.240
50	1053	.294	.245
51	1054	.245	.248
52	1055	.249	.228
53	1056	.220	.244
Mean K(Q-T)		0.238	0.237
Standard deviation		±0.025	±0.021

TABLE III. COMPARISON OF THE K(T-P) VALUES IN THE SITTING AND IN THE RECUMBENT POSITIONS.

NO.	CASE	RECUMBENT K(T-P)	SITTING K(T-P)
1	1002	.694	.687
2	1003	.681	.644
3	1004	.663	.660
4	1005	.705	.732
5	1006	.714	.708
6	1007	.723	.735
7	1008	.648	.707
8	1009	.659	.686
9	1010	.701	.722
10	1011	.672	.694
11	1012	.734	.672
12	1013	.642	.622
13	1014	.648	.671
14	1015	.756	.714
15	1016	.769	.728
16	1017	.712	.685
17	1018	.667	.690
18	1019	.648	.662
19	1020	.710	.714
20	1021	.719	.712
21	1022	.691	.720
22	1023	.694	.661
23	1024	.731	.711
24	1025	.645	.699
25	1026	.672	.678
26	1027	.693	.694
27	1028	.674	.688
28	1029	.642	.657
29	1030	.691	.691
30	1031	.729	.748
31	1032	.716	.688
32	1033	.689	.680
33	1034	.680	.706
34	1035	.662	.683
35	1036	.750	.728
36	1037	.674	.675
37	1038	.691	.691
38	1039	.659	.679
39	1040	.686	.671
40	1041	.680	.666
41	1042	.650	.682
42	1044	.679	.646
43	1045	.716	.681
44	1047	.667	.683
45	1048	.717	.700
46	1049	.729	.691
47	1050	.725	.716
48	1051	.750	.731
49	1052	.695	.770
50	1053	.716	.686
51	1054	.684	.713
52	1055	.694	.721
53	1056	.712	.692
Mean K(T-P)		0.693	0.694
Standard deviation		±0.030	±0.027

$$sd = \sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2} - 2r\frac{S_1 S_2}{N}}$$

$$r = \frac{\frac{\Sigma xy}{N} - M_1 M_2}{S_1 S_2}$$

$$r = +0.648$$

$$sd = 0.004$$

$$t = \frac{M_1 - M_2}{sd} = \frac{0.001}{0.004} = 0.250$$

sd = Standard error of the difference between the means.
S_1 = Standard deviation of K(T-P) (supine).
S_2 = Standard deviation of K(T-P) (sitting).
N, N_1, N_2 = Number of cases.
r = Coefficient of correlation between K(T-P) (supine) and K(T-P) (sitting).
M_1 = Mean K(T-P) (supine).
M_2 = Mean K(T-P) (sitting).

Since t is so small, the difference between the means is not statistically significant.

DISCUSSION

Apparently, the K(Q-T) and K(T-P) values expressing the relationship of Q-T and T-P to the cycle length respectively are not altered merely by changing the position of the subject. It should be noted that our subjects were allowed to remain in the sitting position until the heart rate had become stabilized before tracings were made. As will be pointed out in another report,[5] the changing heart rate is an important factor and must be taken into account whenever the relationships of Q-T and T-P to the cycle length are studied. From these data and calculations it is also seen that there is a significant positive correlation between the K(Q-T) values for both positions, as well as between the K(T-P) values for both positions.

It should be mentioned here that the means for K(Q-T) and K(T-P) found in this series of fifty-three cases are significantly different from the corresponding means found in the previous study.[6,7] However, all of the individual K(Q-T) and K(T-P) values as well as their means fall within the range for normal subjects found in the earlier study; that is, mean ± 2 standard deviation. A number of unavoidable factors entered into this study which are adequate to explain the differences. It is felt, nevertheless, that these deviations do not enter into the consideration of the problem investigated in the present study.

CONCLUSIONS

1. In normal young men there is a significant positive correlation between the K(Q-T) in the supine and sitting positions.

2. There is no significant difference between the K(Q-T) in the supine and sitting positions.

3. There is a significant positive correlation between the K(T-P) in the supine and sitting positions.

4. There is no significant difference between the K(T-P) in the supine and sitting positions.

The author wishes to thank Dr. Arthur C. DeGraff, Professor of Therapeutics at New York University College of Medicine, for having made this study possible and for his helpful suggestions.

REFERENCES

1. Lombard, W. P., and Cope, O. M.: Effect of Posture on the Length of the Systole of the Human Heart, Am. J. Physiol. **49**:140, 1919.
2. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, J. Clin. Investigation **7**:387, 1929.
3. Cheer, S. M., and Li, R. C.: Studies on the Electrical Systole (Q-T Interval) of the Heart. I. Duration of Electrical Systole in Normal Chinese, Chinese J. Physiol. **4**:191, 1930.
4. White, M. S., Kossmann, C. E., and Ershler, I.: The Effect of High Altitude and Rebreathing on the Duration of Electrical Systole in Man, AM. HEART J. **24**:230, 1942.
5. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. V. The Effect of Changing Heart Rate Upon the Q-T Interval and the T-P Interval and Their Respective Relationships to the Cycle Length (R-R Interval). AM. HEART J. In press.
6. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Norman Men. I. The Duration of the Q-T Interval and Its Relationship to the Cycle Length (R-R Interval), AM. HEART J. **31**:329, 1946.
7. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. II. The Duration of the T-P Interval and Its Relationship to the Cycle Length (R-R Interval), AM. HEART J. **31**:464, 1946.
8. Snedecor, G. W.: Statistical Methods, ed. 3, Ames, 1940, The Iowa State College Press.

HEART DISEASE IN THE SOUTH

II. A Statistical Survey of One Hundred Seventeen Deaths Due to Rheumatic Heart Disease

Joe E. Holoubek, M.D., and Alice Baker Holoubek, M.D.
Shreveport, La.

THE prevalence of rheumatic heart disease, particularly in the South, has been the subject of many reports.[1-10] A statistical analysis of 1,045 deaths due to heart disease from the autopsy records of Charity Hospital, New Orleans, La., has been previously reported by one of us (A. B. H.).[1] Because of the large number of deaths recorded due to rheumatic heart disease, a more detailed analysis of these deaths is now presented.

During the period which this study covered 8,313 patients were autopsied, of whom 5,252, or 63.2 per cent, were Negroes. The series included 2,982 Negro men, 2,270 Negro women, 1,975 white men, and 1,086 white women. Death was the result of heart disease in 1,045, or 12.6 per cent, of this entire series. Negroes comprised 63.6 per cent of this latter group.

Of the total group of cardiac deaths, 117, or 11.1 per cent, were classified as due primarily to rheumatic heart disease. This comprises 1.4 per cent of the total autopsy series (Fig.1). As will be seen by the chart, the peaks of incidence occurred between the ages of 10 and 20 years, after which there was a gradual decline. A second peak occurred at the age of 60 years.

Fig. 2 subdivides the incidence of deaths due to rheumatic heart disease into the incidence in the Negro and the incidence in the white race. There were sixty-seven, or 57.3 per cent, deaths in the Negroes, while the remaining fifty were in white persons. It will be seen that the peaks of incidence in the white race occur between the ages of 20 and 25 years; a second peak occurring at 60 years of age. However, in the Negro the peak occurred at the age of 15 years; with another peak present at 45 years. Of the white patients in this group thirty-three were men and seventeen were women. Of the Negro patients thirty-four were men and thirty-three were women.

Other Cardiac Findings and the Site of Valvular Involvement.—Complicating cardiac conditions in the entire group of 117 whose deaths were due to rheumatic heart disease were twenty-one cases of bacterial endocarditis (17.9 per cent), sixteen subacute and five acute; eleven cases of coronary sclerosis; and five cases of hypertension.

From the Department of Medicine of the Louisiana State University School of Medicine, and the Charity Hospital at New Orleans.
Received for publication Jan. 16, 1947.

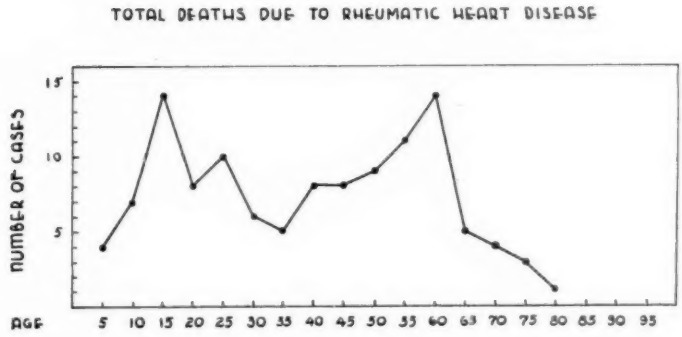


Fig. 1.

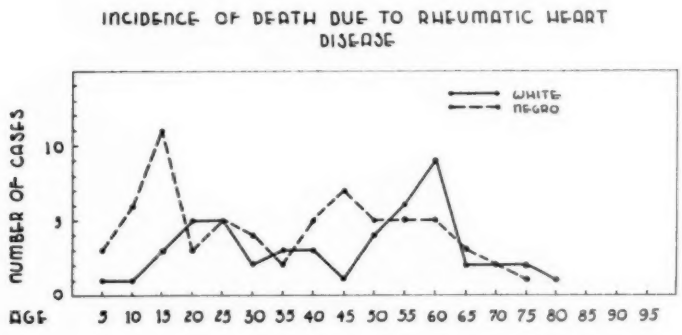

INCIDENCE OF DEATH DUE TO RHEUMATIC HEART DISEASE
WHITE
NEGRO
NUMBER OF CASES
10
5
0
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 2.

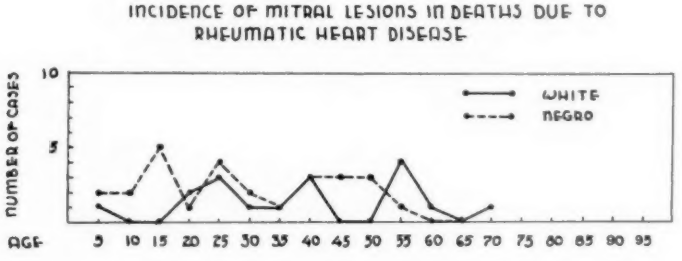

INCIDENCE OF MITRAL LESIONS IN DEATHS DUE TO RHEUMATIC HEART DISEASE
WHITE
NEGRO
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 3.

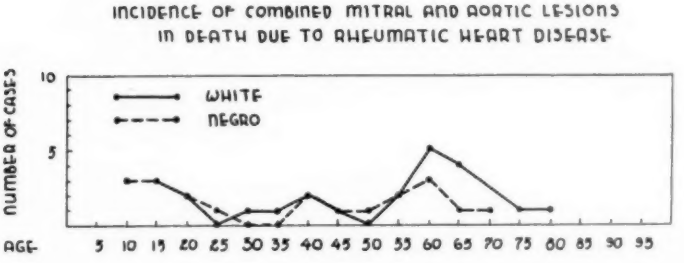

INCIDENCE OF COMBINED MITRAL AND AORTIC LESIONS IN DEATH DUE TO RHEUMATIC HEART DISEASE
WHITE
NEGRO
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 4.

The site of the cardiac involvement by the rheumatic process is shown in Table I. It will be seen that mitral involvement alone was present in the highest percentage of cases.

Further subdividing of the valvular involvement reveals the number of times each valve was involved in the 117 subjects whose deaths were due to rheumatic heart disease. The mitral valve was involved in ninety-six (82 per cent) of these cases, the aortic in sixty (51.2 per cent), the tricuspid in eleven (9.4 per cent), and the pulmonary valve in three (2.5 per cent). There was no definite difference in racial incidence in this particular group (Table II).

TABLE I. SITES OF RHEUMATIC VALVULAR INVOLVEMENT IN ONE HUNDRED SEVENTEEN DEATHS DUE TO RHEUMATIC HEART DISEASE

VALVE	WHITE			NEGRO			GRAND TOTAL	PER CENT
	M	F	TOTAL	M	F	TOTAL		
Mitral	9	8	17	11	18	29	46	39.3
Mitral and aortic	16	7	23	11	7	18	41	35.0
Aortic	4	1	5	6	1	7	12	10.2
Mitral and tricuspid	1	0	1	2	1	3	4	3.4
Mitral, tricuspid, and aortic	1	0	1	2	1	3	4	3.4
Pancarditis	0	1	1	0	3	3	4	3.4
Myocarditis	0	0	0	1	1	2	2	1.7
Aortic, pulmonary, and tricuspid	0	0	0	1	1	2	2	1.7
Mitral and pulmonary	1	0	1	0	0	0	1	0.8
Aortic and tricuspid	1	0	1	0	0	0	1	0.8

TABLE II. INCIDENCE OF VALVULAR INVOLVEMENT IN ONE HUNDRED SEVENTEEN DEATHS DUE TO RHEUMATIC HEART DISEASE

VALVE	WHITE			NEGRO			GRAND TOTAL	PER CENT
	M	F	TOTAL	M	F	TOTAL		
Mitral	28	15	43	26	27	53	96	82.0
Aortic	22	8	30	20	10	30	60	51.2
Tricuspid	3	0	3	5	3	8	11	9.4
Pulmonary	1	0	1	1	1	2	3	2.5

Mitral Involvement: Pure mitral lesions were present in forty-six subjects. In nine there was an associated subacute bacterial endocarditis; in one, acute bacterial endocarditis; in one, rheumatic pneumonia; and in one, coronary sclerosis. There was practically no difference according to race or sex (Fig. 3).

Mitral and Aortic Involvement: In this survey involvement of both the mitral and aortic valves was found frequently, being present in a total of forty-one cases. Complicating factors in this group were: subacute bacterial endocarditis in four cases, acute bacterial endocarditis in four cases, coronary sclerosis in three cases, and hypertensive heart disease in one case. Again there was very little difference in the racial or sexual incidence (Fig. 4).

Aortic Valvular Involvement: There were twelve cases in which the aortic valve only was involved. In all of these there was marked hypertrophy and dilatation of the left ventricle. The majority of these were found in middle-aged subjects, the oldest being 98 years old, and the youngest 27 years of age. One of these had acute endocarditis, two had arteriosclerosis, and two had hypertensive heart disease (Fig. 5).

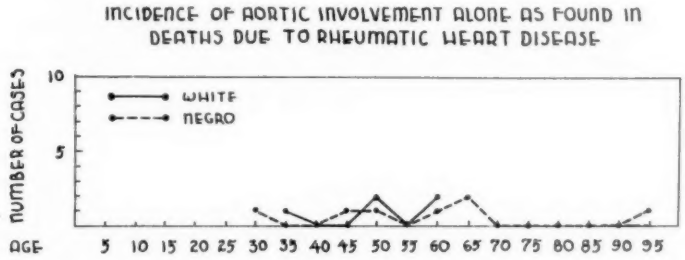

INCIDENCE OF AORTIC INVOLVEMENT ALONE AS FOUND IN DEATHS DUE TO RHEUMATIC HEART DISEASE
NUMBER OF CASES
10
5
WHITE
NEGRO
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 5.

Mitral and Tricuspid Involvement: Mitral and tricuspid involvement was present in only four cases; a white boy, 8 years old, two male Negroes, 11 and 32 years of age, and one Negro woman, 32 years of age. One of the Negro patients had associated syphilitic aortitis.

Mitral, Tricuspid, and Aortic Involvement: Combined mitral, tricuspid, and aortic lesions were present in one 58-year-old white man, in two Negro men, 29 and 54 years of age, respectively, and in one 11-year-old Negro girl.

Pancarditis: Pancarditis was present in one white girl, 17 years of age, and in three Negro women, 12, 41, and 54 years of age, respectively.

Myocarditis: Rheumatic myocarditis alone was present in two Negro patients; one boy, 5 years of age, and one girl, 9 years of age. In both of these the valves were normal.

Aortic, Pulmonary, and Tricuspid Involvement: Combined aortic, pulmonary, and tricuspid involvement was present in two instances; one 59-year-old Negro man, and one 11-year-old Negro girl.

Mitral and Pulmonary Involvement: Mitral and pulmonary valve involvement was present in one white boy, 5 years of age.

Aortic and Tricuspid Involvement: Aortic and tricuspid involvement was present in one white man whose age was 48 years.

COMMENT

Negroes comprised 63.2 per cent of the entire series of autopsied patients. This figure compares almost identically with the percentage of Negroes (63.6 per cent) in the series whose death was due to heart disease. These percentages likewise compare closely with the percentage (57.3 per cent) of Negroes dying of rheumatic heart disease.

The incidence of deaths due to rheumatic heart disease in white subjects showed a ratio of 2 men to 1 woman, while in Negroes this ratio was 1:1. In the total series of autopsied patients, the incidence of men to women was almost 2:1 in white subjects and 1.33:1 in Negroes.

The separation of the deaths due to rheumatic heart disease into the racial incidence reveals that the high peak of deaths in the young group was due to the large number of deaths in Negro girls between the ages of 10 and 15 years. This confirms the statement of Decherd and Herrmann[5] that there is a high incidence of rheumatic heart disease in young Negroes.

The incidence of the valvular involvement follows approximately the same general trend that has been found elsewhere in the country, although the incidence of isolated involvement of the aortic valve is slightly higher in this survey. The mitral valve was, of course, the most commonly involved.

In comparing the age at death of the group having only mitral involvement with that of the group with both mitral and aortic involvement, it will be seen that in the latter group death came at a slightly later age than in the former group.

SUMMARY

In a series of 8,313 patients who were necropsied, death was found to have been the result of heart disease in 1,045 patients. In 117, rheumatic heart disease was present. This series of 117 subjects whose deaths were due to rheumatic heart disease has been analyzed according to sex, age, and racial incidence, and the type of valvular involvement.

The members of the Pathology Department of the Hospital and of the Louisiana State University School of Medicine were very cooperative, and assisted in the study of records which proved difficult to interpret.

Dr. DeWitt T. Baker, New Orleans, assisted in compiling some of the statistical data.

REFERENCES

1. Holoubek, Alice B.: Heart Disease in the South, AM. HEART J. **29**:168, 1945.
2. Camp, P. D., and Glavin, Louise: Rheumatic Fever and Rheumatic Heart Disease in Virginia, Virginia M. Monthly **70**:397, 1943.
3. Baker, L. A.: Analysis of the Etiology in 815 Cases of Organic Heart Disease, Med. Bull. of Veteran's Administration **18**:254, 1942.

4. Claiborne, T. S., and Wolff, B. P.: Rheumatic Heart Disease, South. M. J. **34**:684, 1941.
5. Decherd, G. M., and Herrmann, G. R.: Rheumatic Heart Disease in Texas, Texas State J. Med. **39**:229, 1943.
6. White, P. D.: Heart Disease, ed. 2, New York, 1938, The Macmillan Company.
7. Rowe, Paul: Valvular Heart Disease, Journal Lancet **62**:218, 1942.
8. Shown, A. N.: Rheumatic Heart Disease in Arizona, Southwestern Med. **27**:140, 1943.
9. Hardin, B. L., and Daniels, W. B.: Tricuspid Stenoses, Ann. Int. Med. **17**:536, 1944.
10. Clawson, B. J.: Incidence of Heart Disease Among 30,265 Autopsies, With Special Reference to Age and Sex, AM. HEART J. **29**:607, 1941.

HEART DISEASE IN THE SOUTH

III. An Analysis of Two Hundred Seventeen Deaths Due to Arteriosclerotic Heart Disease

Joe E. Holoubek, M.D., and Alice Baker Holoubek, M.D.
Shreveport, La.

THERE have been many statistical analyses of coronary arteriosclerosis.[1-19] It is evident that in most of these the highest incidence of death from arteriosclerotic cardiovascular disease has been found to occur in the fifth and sixth decades. Most of these studies consider the sexual distinctions in incidence, but few have studied the racial differences.

MATERIAL AND FINDINGS

The material in this paper was gathered from the autopsy records of Charity Hospital at New Orleans from 1935 through 1940. A total of 8,313 autopsies were performed during this period. In 1,045, or 12.6 per cent, of this series death was due primarily to heart disease.

Table I shows the racial and sexual distribution of the total autopsied cases and of the patients whose deaths were due to heart disease. The male sex comprised 67 per cent of the total deaths due to heart disease and 59.6 per cent of the total number of autopsies. Of the cardiac deaths, 217, or 20.7 per cent, were considered to be due primarily to arteriosclerotic heart disease. This comprises 2.6 per cent of the total number of autopsies. The age at death ranged from 30 to 95 years, with the greatest incidence between the ages of 50 and 75 years (Fig. 1).

Fig. 2 illustrates the age at death in white as compared with Negro subjects. One hundred twenty-nine, or 59.4 per cent, of the 217 deaths occurred in the white race, the highest incidence occurring between the ages of 55 to 75 years. In the Negro race the peak incidence occurred between the ages of 45 and 60 years.

Of the group whose deaths were due to arteriosclerosis of the heart and aorta, 117 (53.9 per cent) showed pathologic evidence of myocardial infarction and/or coronary occlusion (Fig. 3). The age range in this group was from 30 to 80 years, with the peak between the ages of 45 and 65 years. In the group whose deaths were due to arteriosclerotic cardiovascular disease without myo-

From the Department of Medicine of the Louisiana State University School of Medicine and the Charity Hospital at New Orleans.
Received for publication Jan. 16, 1947.

AGE AT DEATH OF 217 FATAL CASES OF ARTERIOSCLEROTIC HEART DISEASE

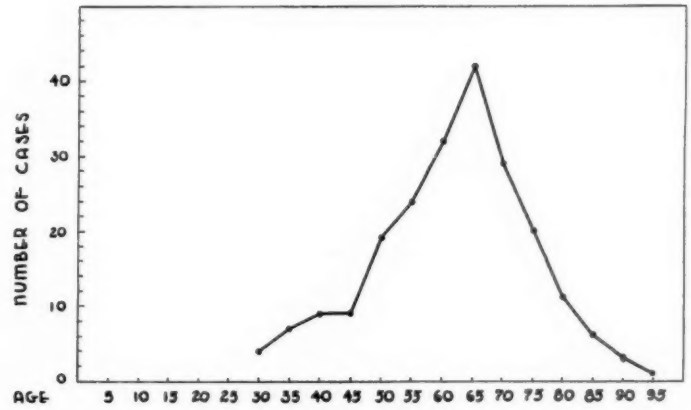


Fig. 1.

INCIDENCE OF DEATH DUE TO ARTERIOSCLEROTIC HEART DISEASE

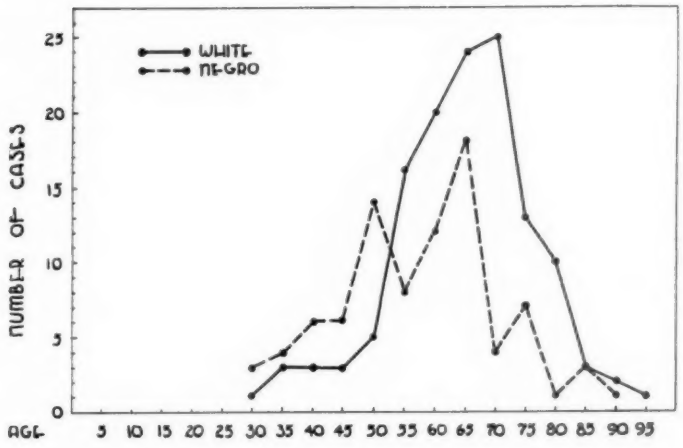


Fig. 2.

ARTERIOSCLEROTIC HEART DISEASE (BOTH RACES) SHOWING THOSE WITH AND THOSE WITHOUT MYOCARDIAL INFARCTION

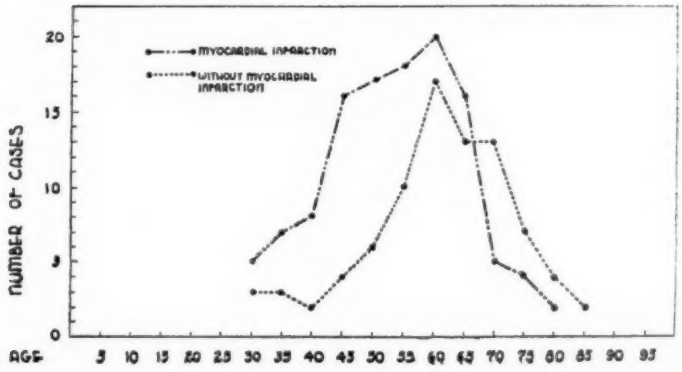


Fig. 3.

TABLE I. RACE AND SEX INCIDENCE IN ROUTINE AUTOPSIES AND IN AUTOPSIES ON PATIENTS WHOSE DEATH WAS THE RESULT OF HEART DISEASE

	NEGRO				WHITE				GRAND TOTAL
	M	F	TOTAL	PER CENT	M	F	TOTAL	PER CENT	
Routine autopsies	2,982	2,270	5,252	63.2	1,975	1,086	3,063	36.8	8,313
Deaths due to heart disease	423	242	665	63.6	281	99	380	37.4	1,045

cardial infarction and/or coronary occlusion, the age at death ranged from 30 to 85, with the greatest incidence between the ages of 55 and 75 years.

In a further study of the 117 autopsied patients who died of myocardial infarction, race and sex are considered. Seventy-three (61.7 per cent) of this group of 117 patients were white persons (Fig. 4.). In this group the age at death in white persons ranged from 30 to 80 years and in Negroes from 30 to 65 years. The highest incidence in white subjects was between the ages of 50 to 65 and in the Negroes between 45 to 60 years.

In differentiating the deaths according to sex (Fig. 5), it is seen that the ratio of men to women is about 7 to 3. There is a rise in incidence in the male group at the age of 30, with a peak occurring between the ages of 55 and 60 years. In the female group there is a rise in incidence at the age of 45 which is maintained until the age of 70 years.

A further differentiation, (Figs. 6 and 7) shows that in the white race there were fifty-five men with autopsy evidence of myocardial infarction as compared to eighteen women. In the women of this series there is very little change in incidence of myocardial infarction throughout the different age groups. However, in the men, there is a marked rise in incidence between the ages of 50 and 65 years. In the Negroes of this series, twenty-seven of the forty-four deaths due to myocardial infarction occurred in men. The incidence of myocardial infarction in Negro women varied only slightly in different age groups. In the male group, however, the incidence reached a peak between the ages of 45 and 55 years.

Of the 117 cases who died of coronary occlusion, hypertension occurred in thirty-five, rheumatic heart disease in three, syphilitic heart disease in two, and diabetes mellitus in one.

Of particular interest were the examples of coronary occlusions which occurred in patients below the age of 40 years. Twelve such cases were found in this study: six in Negro men, two in Negro women, two in white men, and two in white women. The ages of the Negro men were 30, 31, 38, 40, 40, and 40 years, respectively, Negro women, 30 and 35 years, white men, 31 and 32 years, and white women, 35 and 37 years. Hypertension was present in five of these patients, and rheumatic heart disease in two.

There were 100 deaths due to arteriosclerotic heart disease without evidence of myocardial infarction (Figs. 8 and 9). Included in this group were eleven

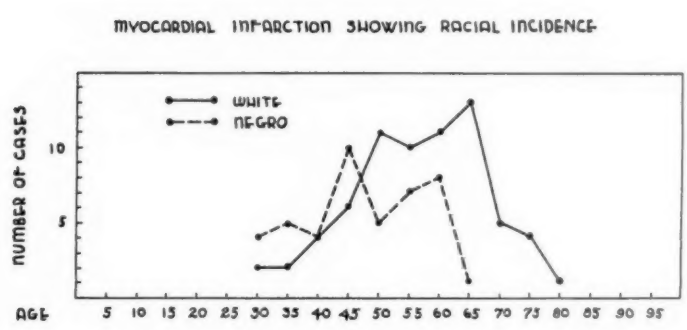

MYOCARDIAL INFARCTION SHOWING RACIAL INCIDENCE
WHITE
NEGRO
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 4.

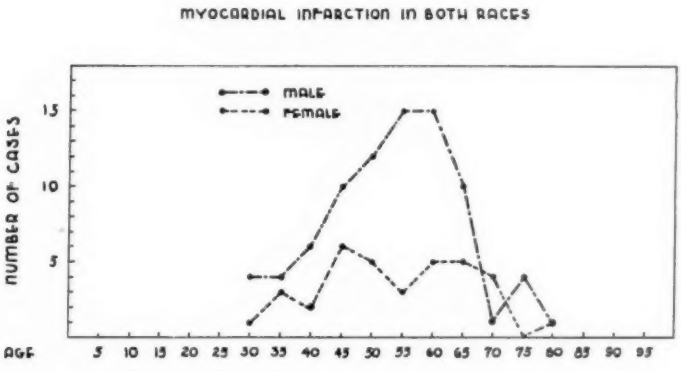


Fig. 5.

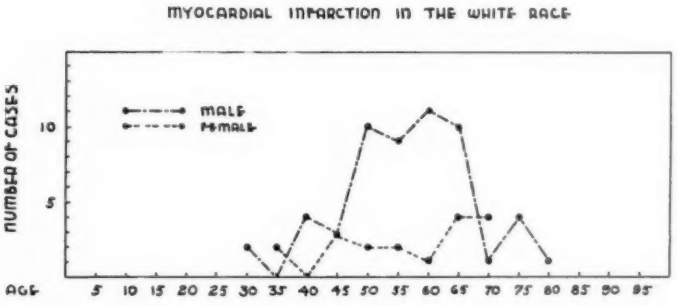

MYOCARDIAL INFARCTION IN THE WHITE RACE
MALE
FEMALE
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 6.

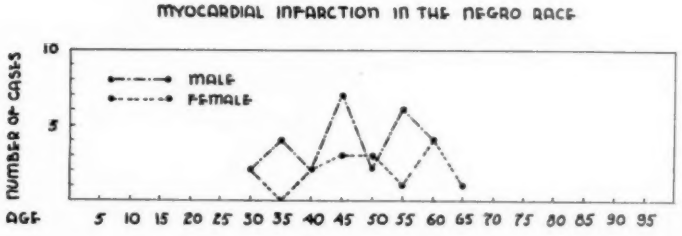

MYOCARDIAL INFARCTION IN THE NEGRO RACE
MALE
FEMALE
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 7.

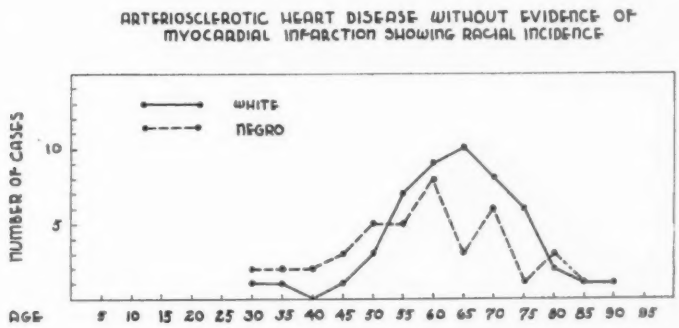

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION SHOWING RACIAL INCIDENCE
WHITE
NEGRO
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 8.

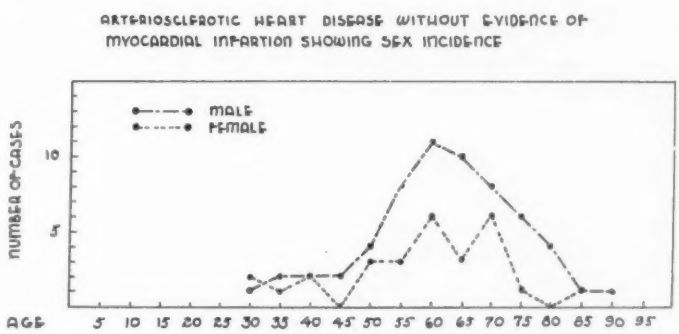

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARTION SHOWING SEX INCIDENCE
MALE
FEMALE
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 9.

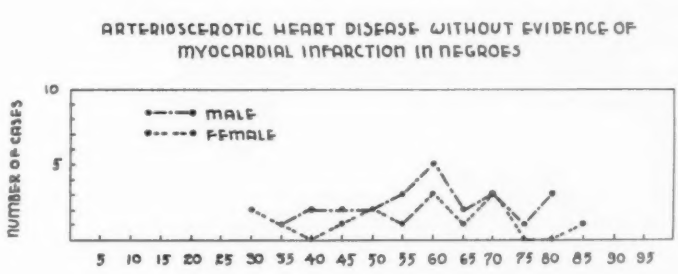

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION IN NEGROES
MALE
FEMALE
NUMBER OF CASES
10
5
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 10.

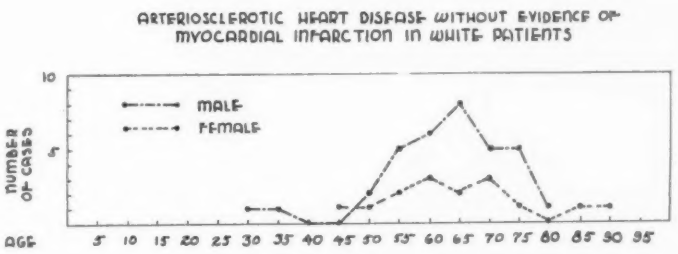

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION IN WHITE PATIENTS
MALE
FEMALE
NUMBER OF CASES
10
5
AGE
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Fig. 11.

cases who died of dissecting aneurysm of the aorta. This comprised 5.1 per cent of the total deaths due to arteriosclerotic cardiovascular disease. These cases of dissecting aneurysm of the aorta have been thoroughly reviewed by Holland and Bayley.[19] Of the eighty-nine remaining cases, fifty (56.1 per cent) were of the white race.

Fig. 10 depicts death due to arteriosclerotic heart disease without evidence of myocardial infarction in the Negroes of this series. There was very little difference in incidence in the two sexes in this group. The incidence showed a slight increase at the ages of 60 and 70 years in both races. In the white race (Fig. 11) it may be seen that thirty-six, 72 per cent, were males, and that the highest incidence in both races was between the ages of 60 and 70.

In the group whose death was due to arteriosclerotic cardiovascular disease without evidence of myocardial infarction the following complications were observed: hypertension in twelve cases, rheumatic heart disease in seven cases. syphilitic cardiovascular disease in one case, and Paget's disease in one case.

SUMMARY

A statistical analysis of 217 deaths due to arteriosclerotic cardiovascular disease at Charity Hospital has been presented and analyzed according to age, sex, and race.

The incidence of death from arteriosclerotic heart disease was found to be higher in the white race than in the Negro race. However, death from this cause occurred at an earlier age in Negroes of this series. Of particular interest is the relatively high incidence of myocardial infarction found in the Negro race, particularly in the younger age groups. The incidence was higher in the male sex in both races. In deaths due to infarction in the white race the ratio of men to women was 3:1, in the Negro race, 1.5:1. In both races the ratio was 2.3:1.

We are indebted to the members of the Pathology Department of the Hospital and of the Louisiana State University School of Medicine who were very cooperative and assisted in the study of records which proved difficult to interpret.

We are also indebted to Dr. DeWitt Baker for his assistance in compiling some of the statistical data.

REFERENCES

1. Holoubek, Alice B.: Heart Disease in the South, I., AM. HEART J. **29**:168, 1945.
2. Gordon, W. H., Bland, E. F., and White, P. D.: Coronary Artery Disease, Analyzed Post Mortem, With Special Reference to the Influence of Economic Status and Sex, AM. HEART J. **17**:10, 1939.
3. Baker, T. W., and Willius, F. A.: Coronary Thrombosis Among Women, Am. J. M. Sc. **196**:815, 1938.
4. Glendy, E. R., Levine, S. A., and White, P. D.: Coronary Disease in Youth, J. A. M. A. **109**:1775, 1937.
5. Wolferth, C. C.: Present Concepts of Acute Coronary Occlusion, J. A. M. A. **109**:1769, 1937.
6. Goldsmith, Grace A., and Willius, F. A.: Bodily Build and Heredity in Coronary Thrombosis, Ann. Int. Med. **10**:1181, 1937.
7. Willius, Frederick A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**:1890, 1936.

8. Levy, Hyman, and Boas, E. P.: Coronary Artery Disease in Women, J. A. M. A. **107**:97, 1938.
9. Levy, R. L., Bruenn, H. G., and Kurtz, Dorothy: Facts on Disease of the Coronary Arteries, Based on a Survey of the Clinical and Pathological Records of 762 Cases, Am. J. M. Sc. **187**:376, 1934.
10. Willius, F. A., Smith, H. L., and Sprague, T. H.: Study of Coronary and Aortic Sclerosis; Incidence and Degree in 5,060 Consecutive Post Mortem Examinations, Proc. Staff Meet., Mayo Clin. **8**:140, 1933.
11. Levy, R. L.: Mild Forms of Coronary Thrombosis, Arch. Int. Med. **47**:1, 1931.
12. Conner, L. A., and Holt, Evelyn: The Subsequent Course and Prognosis in Coronary Thrombosis in an Analysis of 287 Cases, AM. HEART J. **5**:705, 1930.
13. Levine, S. A.: Coronary Thrombosis, Medicine **8**:245, 1929.
14. Christian, H. A.: Cardiac Infarction (Coronary Thrombosis), AM. HEART J. **1**:129, 1925.
15. Nathanson, M. H.: Disease of the Coronary Arteries; Clinical and Pathological Features, Am. J. M. Sc. **170**:240, 1925.
16. Wearn, Joseph T.: Thrombosis of the Coronary Arteries With Infarction of the Heart, Am. J. M. Sc. **165**:250, 1923.
17. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, AM. HEART J. **3**:302, 1928.
18. Claswon, B. J.: Incidence and Types of Heart Disease Among 30,265 Autopsies, AM. HEART J. **22**:607, 1941.
19. Holland, L. F., and Bayley, R. H.: Dissecting, Aneurysm, AM. HEART J. **20**:223, 1940.

Clinical Reports

PAROXYSMAL AURICULAR TACHYCARDIA OF UNUSUAL TYPE

BENJAMIN R. GENDEL, M.D.*
MEMPHIS, TENN.

IN THE majority of instances paroxysmal auricular tachycardia conforms to a typical pattern. It is characterized by a sudden onset, a rapid, highly regular rate, usually between 160 and 180 per minute, and a sudden termination. The disturbed rhythm is transient, lasting from several seconds to a few days. Rarely, it may be prolonged to a few weeks. It may recur repeatedly over a short period of time but usually between attacks there is a prolonged interval which may last for days or years.

Not infrequently, variations from this pattern occur. Cases have been described in which there is slight irregularity of the rate associated with alternation of the cycle length.[1] This type of irregularity cannot be detected clinically. In other cases a more marked irregularity may be present due to auriculoventricular block. When this block is of varying degree, the condition clinically resembles auricular fibrillation. Literature on these cases has recently been reviewed by Barker and associates[2] and by Decherd and co-workers.[3] Fine and Miller[4] and Miller and Perelman[5] reported two patients with an unusual variation, in both of whom paroxysmal auricular tachycardia was precipitated whenever the patient was erect and frequently would disappear on recumbency. These patients and some of those with block showed a persistence of the arrhythmia over a prolonged period of time.

Recently two patients were observed with an unusual type of paroxysmal auricular tachycardia. The rapid heart rate persisted over a period of months and was characterized by recurrent episodes of auricular tachycardia lasting a few seconds, with intervening periods of approximately one-half second between attacks. Because of the unusual nature of this arrhythmia, these cases are being reported.

REPORT OF CASES

CASE 1.—A 25-year-old white man who felt well was found to have an irregular tachycardia on routine examination on May 26, 1945. An electrocardiogram made on May 29, 1945, revealed the arrhythmia to be discussed. He was treated with quinidine sulfate, 0.2 Gm., and pheno-

From the Medical Service, Lovell General Hospital, Fort Devens, Mass.
Received for publication Oct. 17, 1946.
*Formerly Major, Medical Corps, Army of the United States.

barbital, 0.03 Gm., three times daily and later four times daily on several occasions without success. In July, another course of quinidine sulfate, 0.4 Gm., every four hours, was attempted but after several days it was discontinued because of nausea, vomiting, and diarrhea. There was no effect on the arrhythmia. Several courses of digitalis produced a 2:1 A-V block but did not affect the fundamental rhythm. The past and family histories were irrelevant.

The lungs were clear to percussion and auscultation. The pulse was rapid and irregular. The rate was 150 per minute at the wrist and 172 at the apex. The blood pressure was 120/80. The heart size was within normal limits, and there were no murmurs. The heart rate and irregularity did not change after exercise. The liver and spleen were not palpable, and there was no edema. No other significant findings were present.

The basal metabolic rate was −11 per cent. X-ray and fluoroscopic study revealed no enlargement of the heart or its chambers. Many electrocardiograms were taken during the patient's stay in the hospital. These revealed an auricular tachycardia with a rate of 162 to 175 per minute. The tachycardia occurred in short paroxysms lasting about five seconds. After a very brief interval of approximately 0.8 second, a normal sinus beat would occur and this would be followed by another short run of auricular tachycardia (Fig. 1, *A*).

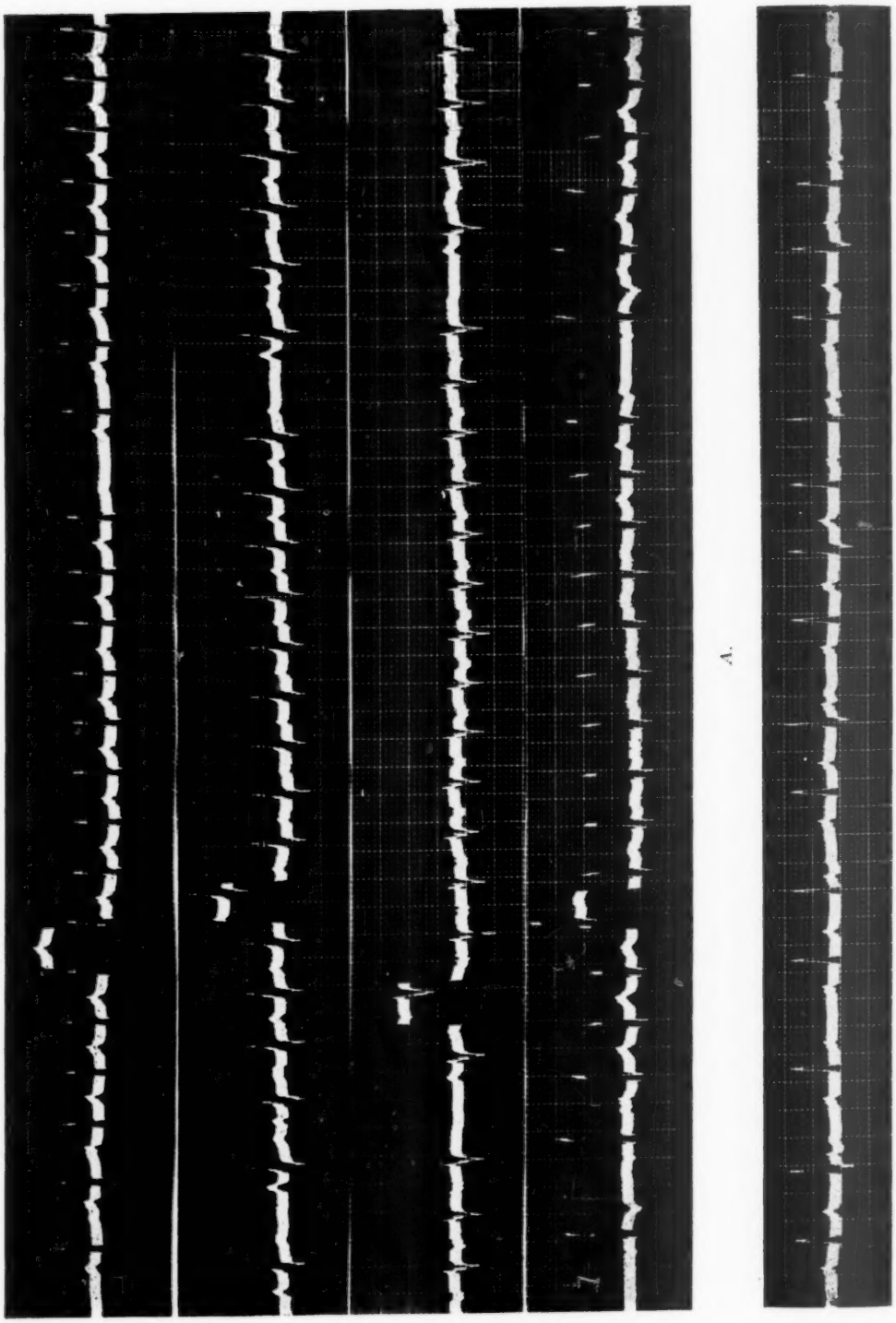
The patient was observed for several weeks without medication. During this time he was able to carry out his routine activities and there was no suggestion of cardiac decompensation. The arrhythmia continued unabated and was present continuously. No change was induced by exercise, breath holding, change of position, or carotid sinus pressure. In September, 1945, he was fully digitalized with digitalis leaf and this caused a slowing of the ventricular rate due to 1:1 to 2:1 A-V block (Fig. 1, *B*). Digitalis was stopped and he was later given 25.0 mg. of mecholyl subcutaneously. A prompt effect was obtained, characterized by profuse sweating and suffusion of the face, chest, and arms, but there was no change in the fundamental rhythm. A course of quinidine, 0.4 Gm. every two hours orally for five doses, was given without effect. A course of potassium salts given orally for several days produced no effect. Digitaline Nativelle, 1.2 mg., was administered intravenously but there was no effect on the rhythm. Digitaline Nativelle, 0.1 mg. orally three times daily, was continued, and in several days 1:1 to 2:1 A-V block appeared. The patient was maintained on a dose of 0.1 Gm. of digitalis leaf, and on Dec. 18, 1945, he received a course of quinidine sulfate, 0.4 Gm. every two hours orally for five doses. That afternoon the rate and rhythm became normal, and an electrocardiogram disclosed the presence of a normal sinus rhythm. The patient was kept on a maintenance dose of digitalis, 01. Gm. daily, until Jan. 7, 1946, when it was discontinued. Subsequent electrocardiograms (Fig. 2) revealed a normal sinus rhythm with slight left axis deviation, slightly depressed S-T segments in Leads I, II, and III, and inverted T waves.

CASE 2.—A 25-year-old white man was found to have an arrhythmia when admitted to the hospital following an injury to the feet, incurred when he fell one and one-half stories to the ground. An electrocardiogram on July 14, 1945, showed the presence of an arrhythmia, to be discussed. The patient was totally unaware of this arrhythmia and had no symptoms referable to the cardiovascular system. Attempts to treat the arrhythmia with digitalis, quinidine, and carotid sinus pressure were unsuccessful. The past and family histories were irrelevant.

The blood pressure was 115/60. The heart was normal in size and position. The rate was 160 per minute and slightly irregular. The liver and spleen were not palpable, and there was no edema. The remainder of the examination was noncontributory.

The basal metabolic rate was normal. X-ray and fluoroscopic examinations of the heart were normal. Electrocardiogram revealed an arrhythmia which was interpreted to show short runs of paroxysmal auricular tachycardia lasting about four seconds, with an interval of 0.5 second between paroxysms. The heart rate was 190 per minute. The intermittence was not due to an A-V block and, unlike Case 1, normal sinus beats did not occur between the short paroxysms (Fig. 3, *A*).

The arrhythmia was not influenced by respiration, change in position, or carotid sinus pressure. The patient was digitalized orally with digitalis leaf with the production of A-V block, and, at times, interruption of the abnormal mechanism and the occurrence of normal sinus beats (Fig. 3, *B*). Digitalis was discontinued and the patient was later given a course of potassium



A. *B.*

Fig. 1.—Case 1. *A*, Nov. 19, 1946. Three standard leads and Lead IV F. *B*, Dec. 15, 1945. Lead I. Auricular tachycardia with varying degrees of partial A-V block.

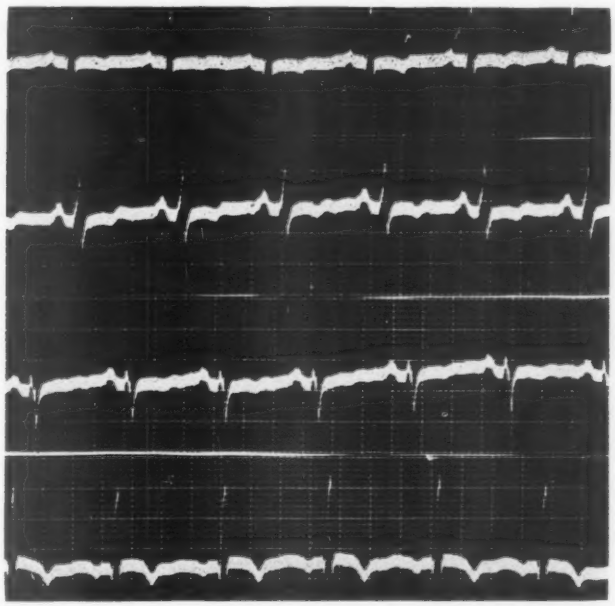


Fig. 2.—Case 1. Jan. 29, 1946. Normal sinus rhythm. There are still S-T segment abnormalities and T-wave inversion. The patient had not had digitalis for three weeks.

salts without any influence on the arrhythmia. On Dec. 6, 1945, he was given 25 mg. of mecholyl without any change.

He was given numerous trials of therapy with quinidine sulfate, 0.4 Gm. orally every two hours for five doses. These were invariably unsuccessful. On Jan. 28, 1946, after a course of quinidine, the patient developed a normal sinus rhythm with a rate of 77 per minute (Fig. 4). However, this was short-lived and the arrhythmia returned on the following morning. Further attempts with a similar course of quinidine, followed by 0.4 Gm. every four hours as a maintenance dose, were fruitless. On this regime, the patient developed A-V block and ventricular premature beats, the latter occurring in groups of two or three. It was felt that further quinidine might result in ventricular tachycardia and this therapy was discontinued. One cubic centimeter of prostigmine 1:2000 was administered subcutaneously without influence on the rhythm. The patient was given Cedilanid, 1.6 mg., intravenously in January, 1946, and this resulted in periods of asystole and auricular tachycardia with varying A-V block. While fully digitalized, another course of quinidine was attempted but did not restore a normal rhythm. The patient was kept on a maintenance dose of digitalis which was of value in that it reduced the ventricular rate.

DISCUSSION

The unusual arrhythmia presented by these two patients who were observed simultaneously had certain clinical characteristics. It was chronic and persisted over a period of months. Despite the persistent rapid cardiac rate, no signs of congestive failure developed although the patients were permitted ordinary activity. There was refractoriness to the usual therapy which is effective in paroxysmal auricular tachycardia. Breath-holding, the Valsalva experiment, change in posture, digitalis, quinidine, and time did not influence the fundamental arrhythmia. In the first patient it was possible after full digitalization

A.

B.

FIG. 3. Case 2. A, November, 1945. Three standard leads and Lead IV F. B, Jan. 15, 1946. Lead II. Paroxysmal auricular tachycardia and A-V block, interrupted by normal sinus beats.

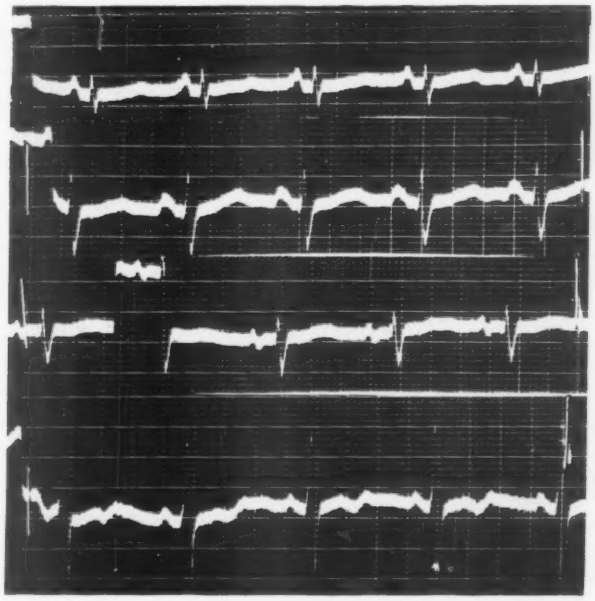


Fig. 4.—Case 2. Jan. 28, 1946. Normal sinus rhythm.

and the simultaneous administration of quinidine to restore the rhythm to normal. In the other patient, many trials of therapy with these methods were unsuccessful. In addition, he received potassium salts orally and prostigmine parenterally with a similar lack of response. On only one occasion, for a short period, was it possible to obtain a normal sinus rhythm by use of quinidine. This could not be repeated subsequently. A-V block was produced by digitalis in both patients.

There was no clinical evidence of heart disease in these patients. It is not known if the injury mentioned in Case 2 precipitated the tachycardia. Repeated physical examination by a number of observers failed to reveal any evidence of cardiac disease. In addition, x-ray and fluoroscopic study and electrocardiograms did not reveal any evidence of heart disease. The persistence of the tachycardia and the refractoriness to therapy are similar to the course in paroxysmal auricular tachycardia with A-V block. Lenhartz and Samet[6] described a patient who had auricular tachycardia with A-V block who had recurrent attacks lasting up to ninety-four days. A patient reported by Maddox[7] had auricular tachycardia which lasted sixty-nine days and was still present on the last examination. Levine[8] mentioned a patient who had a chronic auricular tachycardia, with intermittent A-V block, which lasted for a period of nineteen years. This patient was alive at 72 years of age and was reported to have been ambulatory and without congestive failure during all that time.

The electrocardiograms in these patients bore a superficial resemblance to those of patients with paroxysmal auricular tachycardia with A-V block. The irregularity, however, was due to frequent termination of the paroxysms. In

Fig. 3.—Case 2. A, November, 1945. Three standard leads and Lead IV F. B, Jan. 15, 1946. Lead II. Paroxysmal auricular tachycardia and A-V block, interrupted by normal sinus beats.

the first patient each paroxysm was preceded by a normal sinus beat. In the second patient, normal sinus beats between the short paroxysms occurred only when A-V block was produced by digitalis (Fig. 3, *B*).

SUMMARY

1. Two patients with a chronic auricular tachycardia which consisted of short recurrent attacks of paroxysmal auricular tachycardia are reported on.

2. The condition was refractory to ordinary therapy.

3. In one of the two patients it was possible to revert the rhythm to a normal sinus rhythm by full digitalization followed by the administration of quinidine.

4. In the other patient, the arrhythmia persisted although the ventricular rate could be partially controlled by digitalis.

The author expresses his appreciation to Dr. Louis Wolff, of Boston, Mass., for his advice in the management of these patients and for his criticism of the manuscript.

REFERENCES

1. Barker, P. S., Johnston, F. D., and Wilson, F. J.: Auricular Paroxysmal Tachycardia With Alternation of Cycle Length, AM. HEART J. **25**:799, 1943.
2. Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia With Auriculo-Ventricular Block, AM. HEART J. **25**:765, 1943.
3. Decherd, G. M., Jr., Herrman, G. R., and Schwab, E. H.: Paroxysmal Supraventricular Tachycardia With A-V Block, AM. HEART J. **26**:446, 1943.
4. Fine, M. J., and Miller, R.: Orthostatic Paroxysmal Auricular Tachycardia With Unusual Response to Change of Posture, AM. HEART J. **20**:366, 1940.
5. Miller, R., and Perelman, J. S.: Chronic Auricular Tachycardia With Unusual Response To Change in Posture, AM. HEART J. **29**:555, 1945.
6. Lenhartz, H., and Samet, B.: Quoted by Barker and co-workers.[2]
7. Maddox, K.: Auricular Paroxysmal Tachycardia (Possibly Nomotopic) With Variable Auriculoventricular Conduction Time, AM. HEART J. **14**:183, 1937.
8. Levine, S. A.: Clinical Heart Disease, ed. 3, Philadelphia, 1945, W. B. Saunders Co., Fig. 28, p. 320.

SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNG SIMULATING ORGANIC HEART DISEASE

EDWARD S. MCCABE, M.D.*
BALTIMORE, MD.

IN 1879, Laennec[1] gave the first accurate description of the pathologic anatomy of interstitial emphysema. Müller[2] in 1888 noticed fine, bubbling crepitations occurring synchronously with the heart beat as an early sign of mediastinal emphysema. The diagnosis, however, was only made clinically when air was discovered in the subcutaneous tissues, especially those of the neck, and when trauma or violent effort appeared in the history. Lister[3] reported a single case and described a "pericardial knock," which he thought was due to partial obstruction of the pulmonary artery by tension or distortion caused by displacement of the lung.

It remained for Hamman[4,5] to clarify this condition as a clinical entity and bring out the fact that spontaneous development of the lesion is frequent. Hamman stressed: (a) that no effort need be associated with its onset; (b) that radiation of the pain may simulate angina or coronary occlusion; (c) that there are usually no constitutional symptoms; (d) that a crunching, bubbling, crepitant, clicking, or popping sound may be heard over the heart with each contraction and that this sound is more marked after forced expiration (Hamman's sign); (e) that the area of cardiac dullness is diminished; (f) that pneumothorax may occur, usually on the left; (g) that roentgenogram may demonstrate air in the anterior mediastinum or subpleurally; and finally, (h) that the emphysema may follow the fascial planes and present itself peripherally.

As to pathogenesis, Macklin's[6] work is of great interest. This author postulated that in these cases there is an inherent weakness in the alveolar wall, probably near its origin from the bronchiole. This wall ruptures and the escaped air infiltrates into the connective tissue travelling along the fascial planes toward the mediastinum or toward the visceral pleura. Which phase plays the more prominent role would seem to be determined by the pressure gradient existing within the alveolus at the time of rupture. Macklin[7] has demonstrated experimentally that air tends to travel toward the mediastinum along the sheaths of the arteries, and often there are continuous channels from the peripheral alveoli to the hilus. The interstitial tissue about the bronchi contains no air. Having reached the hilus, air collects in bubbles along the borders of the mediastinum and about the heart vessels, infiltrating the tissues lying between

*From the Department of Medicine, Mercy Hospital, and the University of Maryland School of Medicine, Baltimore.
Received for publication Jan. 3, 1947.

the heart and the anterior chest wall. This distention of the mediastinum often causes pain of an extreme degree, with radiation similar to that of angina pectoris. It may give an alarming feeling of substernal pressure or, at times, a pleuritic pain made worse by deep breathing or coughing. Swallowing or turning the head may intensify the pain. The air may be trapped in the mediastinum and gradually absorbed, or it may burrow to the surface and appear above the clavicles, spreading up the neck and over the front of the chest. It also may go down posteriorly below the diaphragm into the retroperitoneal tissues.

Miller[8] stated that six of eight cases of spontaneous interstitial emphysema that he has seen in three years had a complicating pneumothorax on the left side. Hamman's[5] series shows two out of seven cases with left pneumothorax as a complication. Macklin[7] has demonstrated that it is easy to have air escape from the mediastinum into the pleural space with an intact visceral pleura, but that the reverse is not possible. The probability still exists that air may travel along the interstitial bands of the lung to the pleura and form a subpleural bleb which may rupture. It seems more likely, however, in view of the experimental work, that air reaches the pleural cavity mainly through the mediastinum. The resulting pneumothorax may be of the tension type.

Symptoms and signs suggesting intrapericardial pressure may appear if the air pressure reaches the level of venous and intra-auricular pressure and impedes the filling of the auricles. The predilection for left pneumothorax as a complication may be due to the fact that the heart is anchored, as it were, by the cavae and the stress from the heart beat would be against the left mediastinal wall.

It is conceivable that an element of functional coronary insufficiency could arise and tend to obscure the diagnosis. Unfortunately, electrocardiograms were not taken in many of the reported cases and thus it is not possible to obtain a true incidence of electrocardiographic changes. Clinically, Hamman[5] had three cases that simulated coronary occlusion. Wolferth and Wood[9] and Scott[10] reported several cases with anginal type pain. Lintz[11] points out that pericarditis, dissecting aneurysm, pulmonary infarct, mediastinitis, and intercostal neuritis, as well as angina pectoris and coronary occlusion, must be considered in the differential diagnosis. In Miller's[8] cases with electrocardiograms recorded, the significant changes were flattened T wave in Lead I, with elevated S-T segments and inverted T waves in Leads II and III. These cases, however, were complicated by pneumothorax. Hamman[5] had two cases in which electrocardiograms were taken. The findings were low voltage in all leads, especially in Lead I, and inversion of T wave in Lead II. Hamman reported a single case with inverted T waves in all three limb leads, with return to normal in ten days.

If the theoretical mechanism described in the preceding material is correct, then interstitial emphysema would give rise to right heart stasis from compression of the venous network in the lung proper and, secondarily, of the cardiac thebesian veins and the coronary sinus. Fisher[12] reported a fatal case in a child, and the findings were dilatation of the right ventricle and auricle with the pulmonary vessels compressed. Although the reason is obscure, according to McGuire and Bean,[13] the subpleural bullae tend to develop between the parietal pleura and the pericardium. Thus, air acting as an insulator is probably re-

sponsible for the low voltage in the electrocardiograms and it may be of diagnostic value to measure the difference in voltage between an electrocardiogram taken in the supine position and one in a sitting position with some forward inclination. Fagin and Schwab[14] in a recent review noted electrocardiographic changes of a significant nature in 25 per cent of reported cases. Their article includes a follow-up as regards spontaneous interstitial emphysema; approximately 20 per cent of the known cases were found to have suffered recurrences. One in particular required a therapeutic pneumothorax to promote healing. Fagin and Schwab pointed out that prognosis is excellent, except in infancy.

CASE REPORT

The patient was a 27-year-old white man, who was admitted to Mercy Hospital on June 24, 1946, with a chief complaint of pain in the left shoulder. He was apparently well until 1:00 P.M. on June 24, 1946, when he was seized by a sharp pain in his left shoulder after lifting a case of milk bottles shoulder high. This was one of his daily tasks. He stopped for lunch and while eating, the pain radiated down the left side of his chest to the precordial area. He lost his appetite and decided to lie down awhile in order to ease the pain. When it did not improve, a local

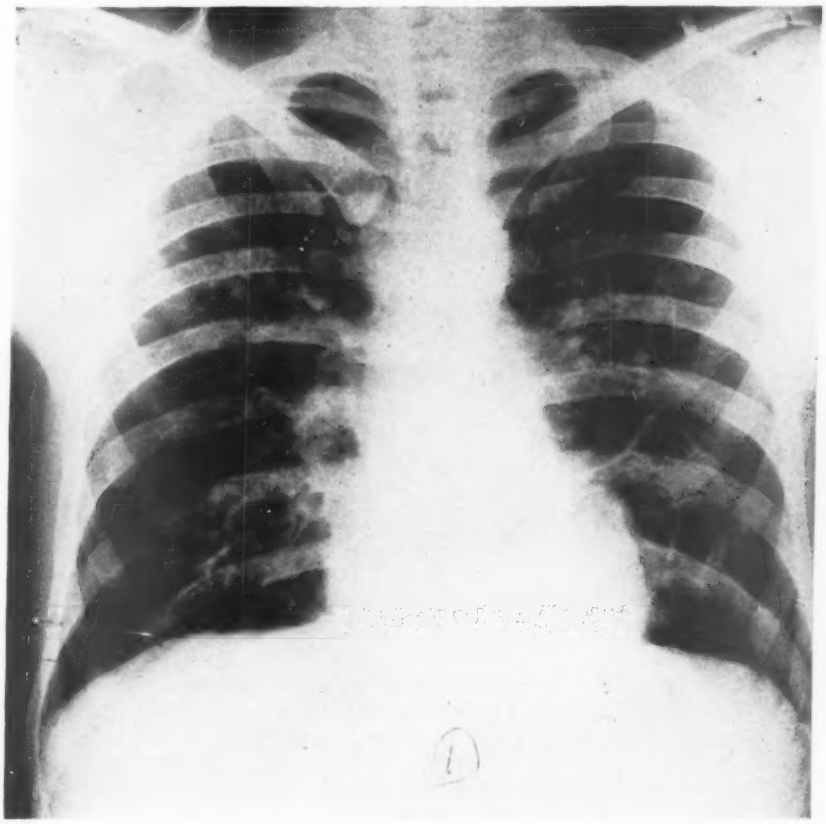


Fig. 1.—There are numerous radiolucent areas (emphysematous blebs) in the lower third of the left lung field.

physician was called who made a presumptive diagnosis of coronary occlusion and arranged for his admission to the hospital.

Systemic review was essentially negative. The past medical history revealed the usual childhood diseases and a few minor injuries, but no serious illnesses. In 1942, however, the patient was turned down by the Armed Forces because of shadows in his lung. In 1945, he had a chest x-ray that was considered clear by the Health Department. Social history and family history were not significant.

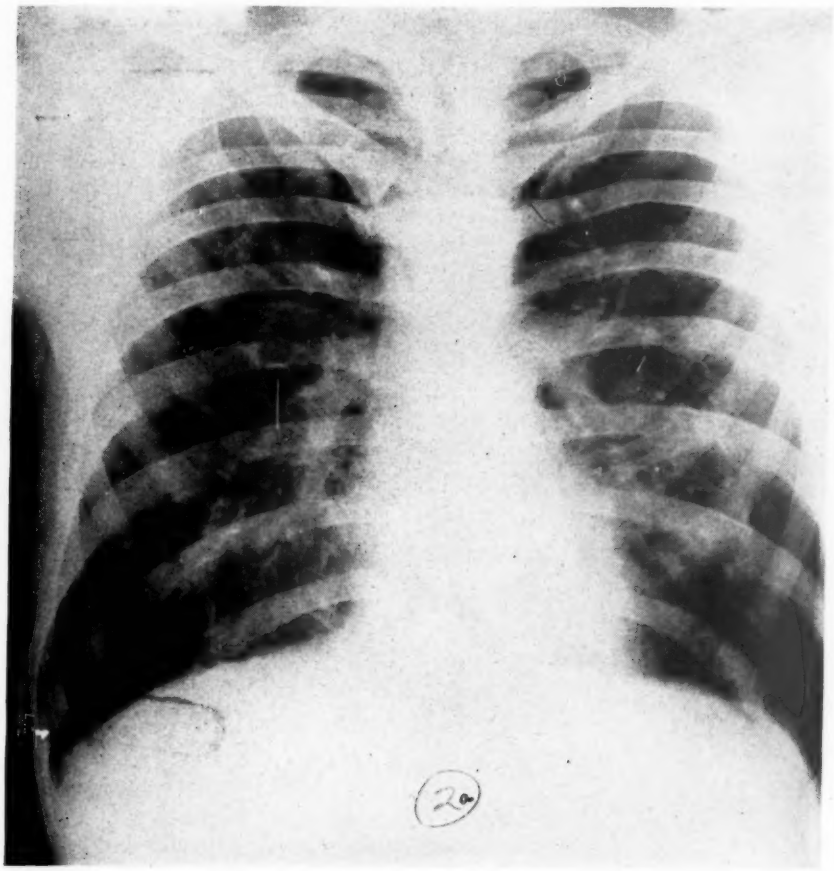


Fig. 2.—*a*, Anteroposterior view shows shift upward in air spaces, suggesting air is free. *b*, Emphysematous areas extending toward hilar region are seen in oblique view.

Physical examination revealed a husky white man in apparent pain. The temperature was 100° F.; pulse, 102; and respirations, 20 per minute. There was moderate dyspnea but no orthopnea. Examination of the eyes showed round, regular, and equal pupils which reacted to light and accommodation. Extraocular movements were normal. Eyegrounds revealed no abnormalities. There was slight hypertrophy of the right tonsil and an injected pharynx. Trachea was in the midline. There was no subcutaneous crepitation. Some cervical adenopathy was found. Thorax was symmetrical. There was a slight respiratory lag on the left, but expansion was good on both sides. Hyper-resonant percussion note on the left obliterated the area of cardiac

dullness at the apex. Breath sounds were diminished on the left, but a few crepitations were present. No heart murmurs were heard. There was rigidity in the epigastrium, probably voluntary; the liver and spleen were not felt. No costovertebral tenderness was elicited. Extremities were negative. Neurological examination was negative.

On June 24, hemoglobin was 16.8 Gm.; erythrocyte count, 7,340,000; and leucocyte count, 24,650, with 91 per cent polymorphonuclear leucocytes, 8 per cent lymphocytes, and 1 per cent eosinophils. Next day, hemoglobin was 16.2 Gm.; erythrocyte count, 5,070,000; and leucocyte

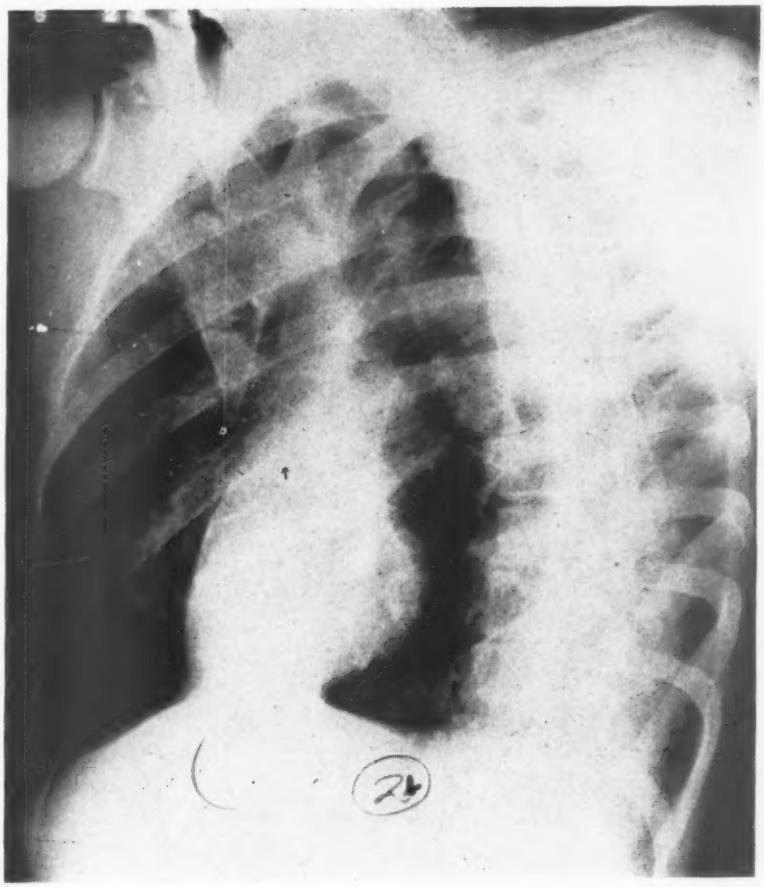


Fig. 2, b.—For legend see opposite page.

count, 12,200, with 69 per cent polymorphonuclear cells. Urinalysis was negative. Cephalin flocculation test was negative in twenty-four hours; 3 plus in forty-eight hours. Prothrombin time was 20 seconds undiluted, and 83 seconds diluted (12.5 per cent). Sedimentation rate corrected was 13 mm. in one hour. Bromsulfalein test was normal. On June 28, hemoglobin was 14.3 Gm.; erythrocyte count, 4,750,000; and leucocyte count, 6,850, with 61 per cent polymorphonuclear cells.

An x-ray of the chest (Fig. 1), on June 25, showed numerous radiolucent areas in the lower third of the left lung field, which had the appearance of emphysematous blebs. The lungs were

otherwise clear, except for fibrous tissue changes in the right axillary region. Heart and aorta were normal. On June 27 (Fig. 2, a and b), x-ray films showed that the emphysematous changes extended from the hilum outward and downward. There had been some shift of the air spaces upward from the diaphragm, suggesting that the air was free. On July 6 (Fig. 3), subpleural blebs were no longer seen in the left chest.

On June 26, venous pressure was 115 mm. of water. The arm-to-lung circulation time (ether) was 10 seconds. The arm-to-tongue time (with magnesium sulfate) was 14 seconds. The vital capacity was 4.6 liters.

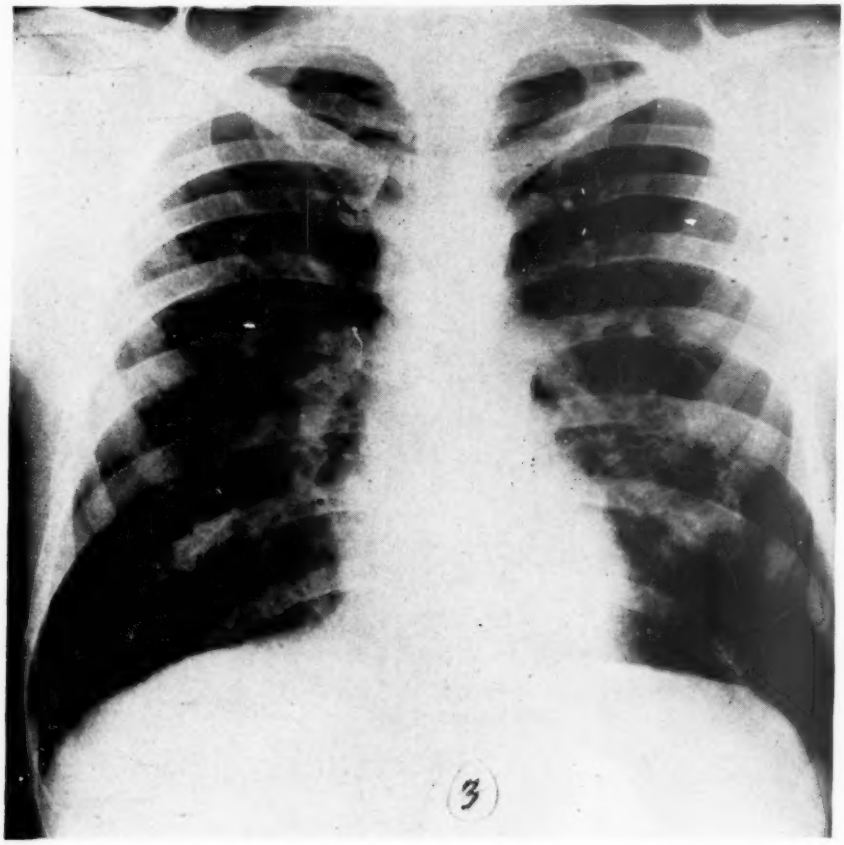


Fig. 3.—Subpleural blebs are no longer seen in left chest.

An electrocardiogram (Fig. 4), taken on June 24, showed sinus arrhythmia, tachycardia, and elevated S-T segments in Leads I, II, and IV. On June 25 (Fig. 5), there was accentuation of S-T segment elevation in Leads I, II, and IV, with an inverted T in Lead III. On June 27 (Fig. 6), the S-T segments were not elevated as much and the T wave was isoelectric in Lead III. On June 29, there was a sinus bradycardia (rate 60 per minute), and the T wave in Lead III was beginning to become upright. On July 2 (Fig. 7), S-T segment changes were within normal limits and T wave was upright and measured 0.2 millivolt.

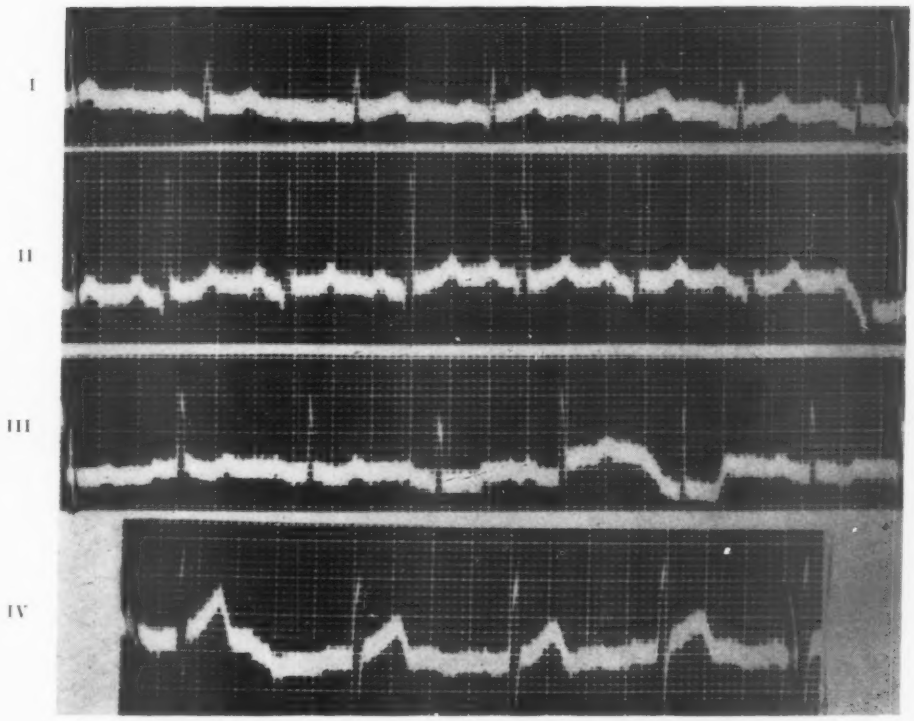


Fig. 4.—June 24, 1946. There is some elevation of S-T segments in Leads I and II.

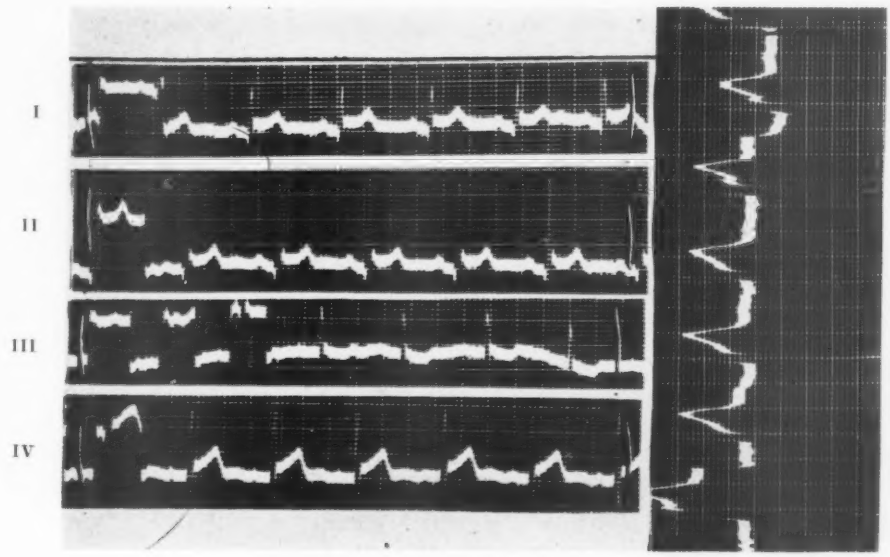


Fig. 5.—June 25, 1946. S-T segment elevation is more marked in Leads I and II.

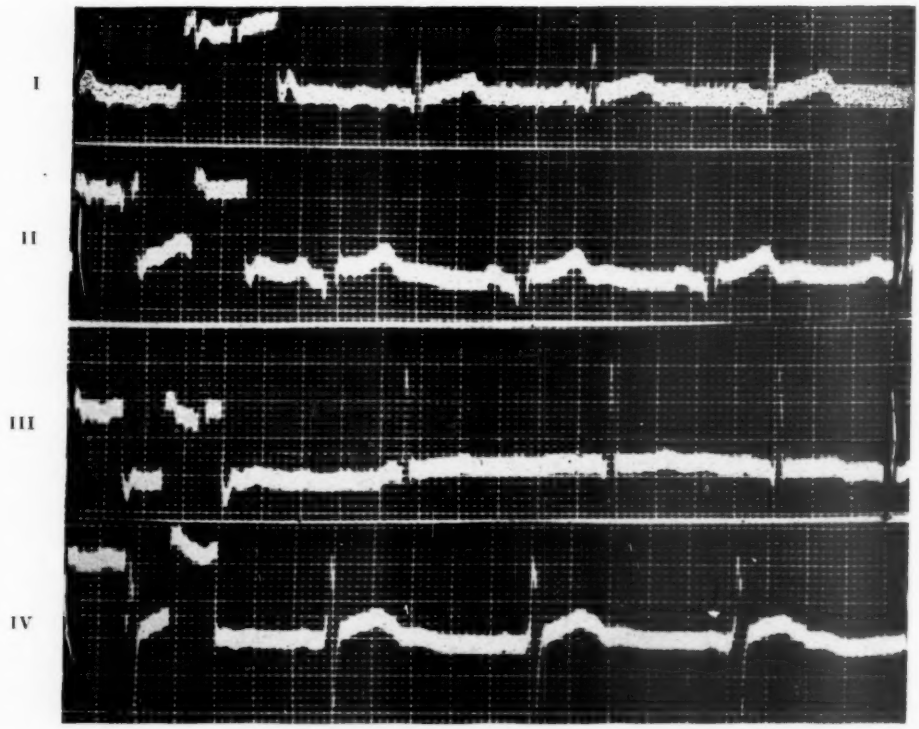


Fig. 6.—June 27, 1946. T waves are diphasic or isoelectric in Lead III, with S-T segments returning to base line in Leads I and II.

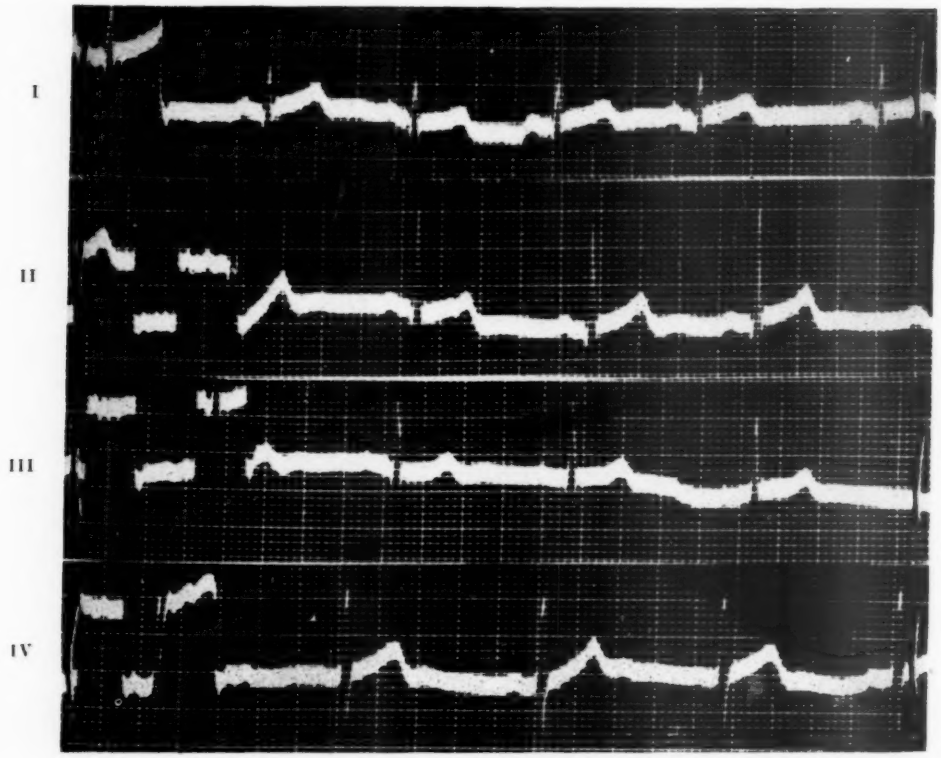


Fig. 7.—July 2, 1946. T wave upright in Lead III. Normal tracing.

DISCUSSION

It is postulated that all degrees of spontaneous interstitial emphysema exist and that the case herein presented was moderate in degree. This patient, a young man, was seen in what was described as an attack of coronary occlusion. The pain was severe enough to require morphine to relieve it. On admission he had a tachycardia with a rate of 102 per minute, a blood pressure of 130/90, moderate dyspnea with mouth breathing, and a very dry tongue. Heart sounds were not heard in the supine position, but were heard in the sitting position; crepitant râles were heard at the left base and were more pronounced during systole and during expiration. The area of relative cardiac dullness was replaced by an area of hyper-resonance. The muscles overlying the epigastric area were tense. An electrocardiogram taken at that time showed slight elevation of S-T segment in Lead I and depression in Lead III. There was leucocytosis, 24,600 with a right shift. Sedimentation rate was 13 mm. corrected. Because of the atypical picture, a chest x-ray was taken and this showed subpleural bullae at junction of parietal pleura and pericardium. Electrocardiogram the next day revealed marked elevation of S-T segments in Leads I, II, and IV, with an inverted T wave in Lead III. X-ray films of the lungs, including an oblique, show a shifting air pattern, although no evidence of pneumothorax or air in mediastinum could be seen.

Considering the fact that his pain was only present intermittently for two days, last showing up in the right shoulder, and that no subcutaneous emphysema could be demonstrated, it is thought the air that escaped into the mediastinum was minimal and in such a location as to remain confined. It was thought quite probable that the initial rent in the alveolar wall would close over early under conservative treatment and hence the air in mediastinum would be reabsorbed rapidly. Then, too, the pains could be due to simple dissection of the interstitial tissues or to functional coronary insufficiency, since venous outflow was impaired.

In four days his leucocyte count had returned to normal, blood pressure was 110/70, and pulse, 60 per minute. The electrocardiogram and prothrombin time were normal by the seventh day. The former showed S-T segment elevations in Leads I, II, and IV within normal limits and an upright T wave in Lead III of 0.2 millivolt. The second electrocardiogram reported would be compatible with pericarditis or anterolateral myocardial infarction. Prothrombin time on admission was 20 seconds undiluted, 75 seconds diluted (12.5 per cent). This is in line with Brambel's[15] theory that the amount of prothrombin itself is relatively constant and that the proportion of activators to inhibitors varies ordinarily. Here it would seem that there was a diminished amount of inhibitors formed or an increased amount of activators liberated. The interstitial air would impair oxygen diffusion and diminish the activity of the reticuloendothelial system in the lung which probably elaborates the inhibitors. Hence, with resorption the prothrombin time returns to normal. It is of interest that neither the vital capacity nor the venous pressure appreciably changed during

the seven days. Circulation times, both arm-to-lung and arm-to-tongue, were slightly longer at the end of the week.

With a past medical history of having been rejected by the Armed Forces in 1942 for lung shadows, it may be that a residual weak area in the wall of an alveolus gave way or that with a transitory atelectasis of one alveolus the adjacent one would be overstretched and the wall would tear. According to Graham and associates,[16] in a severe case prompt measures in instituting decompression of the mediastinum will result in the saving of a life. Whatever the mechanism of its occurrence, it is important to recognize the condition early, since with appropriate treatment, the prognosis is good.

SUMMARY

1. A case of spontaneous interstitial emphysema of the lung is presented and the probable mechanism is discussed.

2. Constitutional symptoms are minimal as a rule, but they vary with the amount of escaped air, as does the duration of the objective findings.

3. Serial roentgenograms are a definite aid in establishing the diagnosis.

4. Organic heart disease is simulated frequently and serial electrocardiograms are in order.

5. Pneumothorax, especially on the left, is a frequent complication.

6. Prognosis is excellent in the majority of cases, except in infancy.

The author wishes to express his appreciation of the stimulating and helpful criticism given by Dr. Maurice C. Pincoffs.

ADDENDUM

Since the preceding case report was prepared four additional cases have been seen on the wards of Mercy Hospital. These were evenly distributed as to sex and all were in the third decade of life. One male and one female had evidently recurrent attacks. The presenting complaint was a sharp pain, sudden in onset, and felt usually in left shoulder area, moderate dyspnea, tachycardia, and a peculiar crackling sound over the precordium. Three cases had a left pneumothorax with 10 to 20 per cent collapse of the upper left lobe. One in particular could not be seen on an anteroposterior roentgenogram, and it was only after a film was obtained in the left anterior oblique position that the 10 per cent collapse was seen. All four did show some air in the posterior mediastinum in the latter view. A positive Hamman's sign was present for from two to five days, but after the first few days it could be demonstrated only when certain positions were assumed. The initial electrocardiograms in the supine position showed low voltage in all leads, especially Lead I, and diphasic and flattened T waves in Leads II and III were observed in two patients. With the tracing taken in the upright position, the voltage of the QRS in Lead I was trebled. With resorption of air, the voltages did not change significantly with position and the T waves became upright. One patient, a 28-year-old white man, had an electrocardiogram that showed a wandering sinus pacemaker, and within five days the tracing shifted back to sinus rhythm. The patients were all treated conservatively and kept at bed rest until the air was absorbed. Then, an additional period of two weeks was advised with a gradual return to normal activity. After a minimum of six months, no case of recurrence has been found in follow-up study.

REFERENCES

1. Laennec, R. T. H.: Traite de L'Auscultation Mediate, Paris, 1879, Asselin et Cie.
2. Müller, F.: Ueber Emphysem des Mediastinum, Klin. Wchnschr. **25**:25, 1888.
3. Lister, W. A.: Case of Pericardial Knock Associated With Spontaneous Pneumothorax, Lancet **1**:1225, 1928.
4. Hamman, L.: Remarks on the Diagnosis of Coronary Occlusion, Ann. Int. Med. **8**:417, 1934.
5. Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **66**:1, 1939.
6. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels From Alveoli to Mediastinum: Clinical Implications, Arch. Int. Med. **64**:913, 1939.
7. Macklin, C. C.: Pneumothorax With Massive Collapse From Experimental Overinflation of the Lung Substance, Canad. M. A. J. **36**:414, 1937.
8. Miller, H.: Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease, Am. J. M. Sc. **209**:211, 1945.
9. Wolferth, C. C., and Wood, F. C.: Angina Pectoris, M. Clin. North America, **13**:947, 1930.
10. Scott, A. M.: The Significance of the Anginal Syndrome in Acute Spontaneous Pneumomediastinum, Lancet **1**:1327, 1937.
11. Lintz, R. M.: Spontaneous Mediastinal Emphysema, Arch. Int. Med. **71**:256, 1943.
12. Fisher, J. H.: Spontaneous Pulmonic Interstitial and Mediastinal Emphysema in an Infant, Canad. M. A. J. **44**:27, 1941.
13. McGuire, J., and Bean, W. B.: Spontaneous Interstitial Emphysema of the Lung, Am. J. M. Sc. **197**:502, 1939.
14. Fagin, I. D., and Schwab, E. H.: Spontaneous Mediastinal Emphysema, Ann. Int. Med. **24**:1052, 1946.
15. Brambel, C. E.: Personal communication to the author.
16. Graham, E. A., Singer, A., and Ballon, H. C.: Surgical Diseases of the Chest, Philadelphia, 1935, Lea & Febiger.

REACTIONS TO DECHOLIN IN CIRCULATION TIME DETERMINATION

JAMES K. NORMAN, M.D.*
FORT WORTH, TEXAS

IN 1931, Winternitz[1] and others introduced Decholin as a substance to be used in the determination of circulation time. It has been used extensively. Decholin† is the sodium salt of dehydrocholic acid, an oxidative product of cholic acid which is derived from natural bile acids. Each cubic centimeter of Decholin contains 20 per cent sodium dehydrocholate. The manufacturers[2] state that "Intravenous use should be undertaken cautiously with the usual observation of the patient and aseptic technique. The parenteral administration of this solution is contraindicated in the presence of bronchial asthma, allergic phenomena, mechanical biliary obstruction, or severe hepatitis."

The Decholin method is usually empolyed in the following manner: with the patient resting in the recumbent position, the skin of the antecubital space is prepared with alcohol. A vein in the antecubital space is selected and entered by means of an 18-gauge needle. Four cubic centimeters of Decholin are rapidly injected into the vein. The time from the beginning of the injection until the patient experiences a bitter taste is measured accurately with a stop watch. This is recorded as the arm-to-tongue circulation time.

The average time obtained in normal subjects with this method is 15 seconds. About 18 seconds is considered prolonged and pathologic. It reflects the blood flow from the arm vein to the right heart, through the lungs, left heart, and arterial system to the tongue. Because it is a subjective test and depends on cooperation of the patient its use is somewhat limited.

In my own personal experience in at least 1,000 such tests, the method has been satisfactory. No untoward effects were encountered until the reactions which are to be reported were observed. It is considered significant that the material which produced reactions in the first two patients was from the same supply of Decholin, while that administered to the third patient was from a different supply. Search of the literature has failed to reveal a report of any such reactions to Decholin. Lederle Laboratories[3] state that they have encountered no similar reactions, nor have any been reported to them.

CASE HISTORIES

CASE 1.—E. M. was a retired white seaman, 74 years of age. He was admitted to the U. S. Marine Hospital, Stapleton, New York, on April 6, 1946, with the history of gradually increasing

From the Medical Department, U. S. Marine Hospital, Stapleton, New York, the Harris Clinic, Fort Worth, and the Harris Memorial Methodist Hospital, Fort Worth.
Received for publication Oct. 15, 1946.
*Former S. A. Surgeon, U. S. Public Health Service, now in the Department of Medicine, Harris Clinic, Fort Worth.
†Decholin is sold in this country by Lederle Laboratories, Inc., under the name of sodium dehydrocholate solution.

dyspnea for the last year and occasional swelling of the feet and ankles. For one week, prior to admission, he had a nonproductive cough and low-grade fever. He gave no history of allergy. Physical examination revealed a thin, emaciated, elderly white man, who appeared chronically ill. Blood pressure was 142/82. The temperature was 100.8° F., pulse, 96, and respirations, 20 per minute. The neck veins were not engorged. The chest was symmetrical. Bilateral expansion was equal. Resonance, fremitus, and breath sounds were normal. There were numerous râles in both bases, more marked on the right. The heart was not enlarged. The rhythm was regular. The sounds were of poor quality and a soft aortic systolic murmur was heard. The abdomen was flat. The liver was not enlarged. There was slight pitting edema of both feet and ankles.

Determination of the circulation time was performed in the usual manner. The first attempt, using the right antecubital vein, was not successful because about half of the testing material was extravasated into tissue outside the vein. The left arm was then used and a satisfactory test obtained. The arm-to-tongue circulation time was found to be 26 seconds. Electrocardiogram showed changes compatible with diffuse coronary artery disease, but there was no evidence of frank infarction. X-ray films of the chest showed no abnormalities of the lung fields and the heart was not enlarged. This patient was digitalized, given chemotherapy, and supportive treatment. He showed definite improvement. One week later the test for circulation time was again performed. The left antecubital vein was again used and the test performed in the usual manner. Within two minutes after the test the patient went into shock, with unconsciousness, rapid rate of pulse, and profuse sweating; the blood pressure was unobtainable. He was given 7½ grains of caffeine sodium benzoate and 5 minims of adrenalin. He responded in about one minute. About five minutes after the test it was noted that the right antecubital space, the site of the original extravasation of Decholin, was markedly edematous, reddened, and pruritic. Three days later, skin tests for sensitivity to Decholin were performed, using 0.1 c.c. of undiluted Decholin injected intradermally in the volar surface of the left forearm. This evoked a marked local response with redness, swelling, and itching. The same test on a control subject was negative. Two days later, the test was repeated on the patient, but this time he was premedicated with benadryl, 50 mg., about one hour prior to the test. Again, a marked local response was noted.

CASE 2.—P. W. was a white merchant seaman, 42 years of age. He had always been in good health until about one year before admission, when he had virus pneumonia. He gave no history of allergy. He was admitted to U. S. Marine Hospital, Stapleton, on May 2, 1946, with the complaint of nonproductive cough and dyspnea for one week. The day before admission, he developed fever which rose to 101° F., with occasional profuse sweating and substernal tightness.

Physical examination revealed a pale, fairly well-developed white male, who appeared to be ill. His temperature was 100.6° F., and respirations, 18 per minute. The throat was negative. The heart was not enlarged. The rhythm was regular and the sounds were of good quality. The heart rate was 96 per minute. The blood pressure was 124/76. No murmurs, thrills, or friction rubs were heard. Expansion of the chest was equal. Expiration was somewhat retarded bilaterally. There was normal resonance and fremitus. Coarse sticky râles were heard throughout both lungs. The liver was not enlarged. The neck veins were not engorged and there was no edema.

Because of the dyspnea, it was thought advisable to determine the circulation time. It was found to be 15 seconds. About one minute after the injection of Decholin the patient had a violent asthmatic attack, which was immediately relieved by 5 minims of adrenalin. He had no recurrence of such an attack. X-ray films of the chest and electrocardiogram were subsequently negative. He received treatment for asthmatic bronchitis and made an uneventful recovery.

CASE 3.—E. C., a 64 year-old white man, a bookkeeper, entered Harris Memorial Methodist Hospital, Fort Worth, on July 31, 1946, for hernioplasty. Medical consultation was requested because medium râles were heard in the right lung base. The patient stated that he had been feeling well and had no cough, fever, or dyspnea. He gave no history of allergy.

Examination revealed him to be a well-developed, well-nourished white man. He did not appear acutely or chronically ill. Positive physical findings were confined to chest and right inguinal region. The thorax was symmetrical. Bilateral expansion was equal. The breath sounds,

resonance, and fremitus were normal throughout the chest. In the right base numerous medium râles were heard which did not disappear on coughing. There were a few similar râles in the left base which did disappear on coughing. The heart was not enlarged. The point of maximum impulse was in the left fifth intercostal space in the mid-clavicular line. The heart rhythm was regular and the rate was 72 per minute. There were no thrills or friction rubs. There was a soft aortic systolic murmur heard in the second intercostal space, just to the right of the sternum. Blood pressure was 110/75. There was no engorgement of the veins of the neck. The liver was not enlarged and not tender. There was no edema. There was a large reducible right indirect inguinal hernia and hydrocele about the size of a lemon. Pulse, temperature, and respiration, two days prior to our examination, had been normal. X-ray films of the chest showed the heart to be of normal size, but the aorta was moderately widened and tortuous. In the region of the right hilus there was an area of patchy increased density which extended down to the right base. Electrocardiogram was negative.

Determination of circulation time was performed in the usual way with Decholin, and found to be 14 seconds. About five minutes after injection of the Decholin he developed a widespread, diffuse urticaria. He was immediately given 50 mg. of benadryl, and within ten minutes the pruritus disappeared, but the urticarial wheals remained for about forty minutes.

COMMENT

We are unable to adequately explain the reactions, but they were definitely of an allergic nature. None of these patients had a history of allergy; although Case 2 had asthmatic bronchitis at the time of the test. It seems unreasonable to assume that there was primary reaction to Decholin per se, unless foreign protein contaminants were present. We were unable to obtain a precipitate after heating a sample of Decholin following addition of acetic acid. The reaction in Case 1 was typically anaphylactoid in nature and may represent a combination of the drug with a haptene with subsequent sensitization. Damaschek[4] put forth this idea as the possible explanation of certain drug reactions in the production of certain blood dyscrasias (agranulocytosis).

SUMMARY

1. The histories of three patients who suffered three different types of allergic or allergic-like reactions to Decholin, when used in circulation time determinations, are presented.

2. It is concluded that: (a) Decholin, as used in the determination of circulation time, is capable of producing allergic-like reactions. (b) No patient with a history of allergy should be subjected to the Decholin method of determining the circulation time. (c) By eliminating those patients with asthma, much of its value is lost. (d) Allergy or allergic-like reactions may occur in patients without history of allergy. (e) Patients may be sensitized to Decholin and at least potentially dangerous consequences may result.

REFERENCES

1. Winternitz, M., Deutsch, J., and Brull, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutemlaufszeit mittels Decholinjektion, Med. Klin. 27:986, 1931.
2. Brochure on Decholin published by Lederle Laboratories, Inc., 1944, New York.
3. Personal communication from Lederle Laboratories, Inc.; June, 1946, New York.
4. Damaschek, W.: Oxford Monographs on Diagnosis and Treatment: Oxford University Press, New York.

BACILLUS COLI ENDOCARDITIS

Review of the Literature With Report of a Case*

D. E. Fletcher, Ph.D.
Little Rock, Ark.

HARRIES and Burtenshaw[1] in 1937 reviewed the literature of endocarditis produced by the coliform bacillus. According to these writers, positive blood cultures for *Bacillus coli* before death and from the heart vegetation after death, together with Gram stains on histologic sections of the vegetation showing gram-negative bacilli in significant numbers, should be the criteria used in establishing a case of endocarditis as due to *Bacillus coli*. They emphasized the ease with which *Bacillus coli* contamination may occur at autopsy. This postulate is both reasonable and sound.

Harries and Burtenshaw, using this standard, accepted five cases from those reported in the literature and added a sixth case. Those included were as follows: Horder[2] in 1908 reported a case of endocarditis which occurred in a 12-year-old boy. The duration of the illness was four months. The pathologic findings at autopsy were a large, friable vegetation on the aortic valve, splenomegaly, embolic phenomena, and peritonitis. A pure culture of *Bacillus coli* was obtained from the vegetation. Dickar[3] in 1932 reported two cases of acute bacterial endocarditis in elderly persons in which *Bacillus acidi lactici* was isolated by ante-mortem blood culture and gram-negative rods were demonstrated in the vegetation. The aortic valve was involved in both cases while the mitral and tricuspid valves were involved in only one. The brain in one case showed multiple infarcts which resulted from septic emboli. Duhig[4] in 1933 reported one case of acute endocarditis in a 25-year-old woman. *Bacillus coli* was isolated by culture from the blood stream ante mortem and from the vegetation post mortem. The anterior cusp of the mitral valve was completely involved by a large vegetation which extended on to the left atrial wall. The posterior cusp of the mitral valve and the remaining heart valves were not damaged. The following year (1934) Crawford and Cruickshank[5] reported a case of acute endocarditis in a woman, 43 years of age, in which *Bacillus acidi lactici* were isolated from the blood stream before death and from the vegetation on the mitral valve and from the spleen at autopsy. The case of endocarditis studied by Harries and Burtenshaw[1] in 1937 occurred in an 18-year-old girl. Both cusps of

From the University of Arkansas School of Medicine, Department of Pathology.
Received for publication Sept. 11, 1946.
*Research paper No. 846, Journal Series, University of Arkansas.

the mitral valve, the attached chordae tendineae, and the auricular wall were involved by a large, deep red, friable vegetation. They cultured gram-negative bacilli from this vegetation. Clumps of short and coccoidal gram-negative rods were demonstrated in the fibrin thrombus on the mitral valve, and in the infarcts in the kidneys. Repeated ante-mortem blood cultures were negative.

Several cases of bacterial endocarditis in which *Bacillus coli* was assumed to be the etiological agent are present in the literature. However, due to either incomplete or inaccessable data they cannot reasonably be accepted as bacteriologically substantiated. They are as follows: Dickar[3] in 1932 referred to cases of *Bacillus coli* endocarditis reported by Lenhartz,[6] Jacob,[7] Jockmann,[8] and Summa.[9] The records of these cases, except that of Jacob, are obscure and the latter's study deals primarily with *Bacillus coli* septicemia. Norris[10] in 1911, in his book on cardiac pathology, stated that in sixty-six cases of endocarditis in which cultures were obtained from the heart's blood and from the vegetations on the heart valves, nine were positive for *Bacillus coli communis*. Norris did not substantiate this statement with specific cases. Thayer[11] in 1926, in his monograph on bacterial endocarditis, mentioned "one or two cases" in which *Bacillus coli* was obtained from the vegetations. He also referred to one case of Harbetz[12] in which gram-negative rods were obtained at necropsy. Obviously, such statements do not constitute case reports and should be included in any study with reservation. Cowan[13] in 1927, in his treatise on acute endocarditis, stated that *Bacillus coli* was the etiological agent in two out of his series of 430 cases. He did not give complete data on these two cases. Phipps[14] in 1932 reported a series of forty-four cases of acute bacterial endocarditis in which positive blood cultures for *Bacillus coli* were obtained in five. No mention was made as to whether gram-negative organisms were present in the vegetations. The mitral valve was involved twice, the aortic and mitral valves together once, and all three valves once. Inasmuch as *Bacillus coli* septicemia is of frequent occurrence, positive cultures for *Bacillus coli*, regardless of whether they are taken from the circulating blood or directly from the vegetation, are of questionable significance unless gram-negative rods are demonstrated in histologic sections of the vegetation. Table I summarizes the data pertaining to the valvular involvement in *Bacillus coli* endocarditis.

Apparently no cases of *Bacillus coli* endocarditis have been reported since 1937. The writer is reporting a recent case of acute bacterial endocarditis from which three positive blood cultures for *Escherichia coli* were obtained during life, and at autopsy large colonies of gram-negative rods compatible with *Escherichia coli* were demonstrated in multiple histologic sections from the vegetation on the mitral valve, from infarcts in the spleen and kidneys, and from thrombi in the common iliac arteries.

CASE REPORT

M. D., a white woman 30 years of age, was admitted to the University Hospital on Nov. 11, 1945, in shock. She had been hospitalized and treated for "strep throat, pneumonia, and blood poisoning" in July, 1945. A curettage was performed on Sept. 18, 1945, in an attempt to correct excessive vaginal bleeding. On Sept. 2, 1945, the patient was operated upon for a tubal

TABLE I. VALVULAR INVOLVEMENT IN PROVEN CASES OF BACILLUS COLI ENDOCARDITIS

AUTHOR	YEAR REPORTED	NO. OF CASES	VALVES INVOLVED			
			MITRAL	AORTIC	TRICUSPID	PULMONARY
Horder[2]	1908	1		Aortic		
Dickar[3]	1932	2	Mitral	Aortic Aortic	Tricuspid	
Phipps[14]	1932	5	Mitral Mitral Mitral Mitral	Aortic Aortic	Tricuspid Tricuspid	
Duhig[4]	1933	1	Mitral			
Crawford and Cruickshank[5]	1934	1	Mitral			
Harries and Burtenshaw[1]	1937	1	Mitral			
Fletcher	1946	1	Mitral			
Total		12	9	5	3	0

pregnancy. The wound failed to heal. On Nov. 4, 1945, the patient began to vomit and to have rigors. The vomiting and rigors increased in severity, her condition became critical, and she was brought to the University Hospital.

On admission, the temperature by axilla was 103° F.; pulse, 148 per minute; respiration, 40; and blood pressure, 76/44. The abdomen was tender to palpation and slight muscle guard was evident. A draining sinus was present in the operative scar in the mid-lower abdominal wall. The liver was enlarged to percussion. The lungs were normal. The heart was normal in size, the rhythm was regular, the rate was rapid. The quality of the heart sounds was good and no murmurs were detected. Decubitus ulcers were present in the sacral region.

Laboratory studies showed a negative urinalysis, hemoglobin, 6 Gm., red blood cell count of 2,750,000, and a white blood cell count of 23,150, with 72 per cent polymorphonuclear leucocytes. The differential count showed a slight shift to the left. The Wassermann examination was negative. A blood culture taken on admission was positive for *Escherichia coli*.

The patient remained in the hospital sixteen days during which time her condition remained critical. She was irrational, had urinary and fecal incontinence, marked edema of the extremities, repeated rigors, clinical signs of meningitis, labored respirations, and increasing abdominal distention. Her skin had a café-au-lait pallor and petechiae appeared over the face and extremities. The axillary temperature fluctuated between 99° and 106° F., the pulse between 100 and 160, respiration between 20 and 50 per minute, and the blood pressure varied between 83/42 and 108/56. The specific gravity of the urine varied between 1.003 and 1.014 and the nonprotein nitrogen ranged between 50 and 112 mg. per cent. The plasma protein varied between 4.1 and 4.4 grams. The blood chlorides were 480 mg. per cent. Hemoglobin values varied from 6 to 11.75 grams. The total red blood cell count showed variations from 1,750,000 to 4,030,000 with transfusions, and the white blood cell count, 16,750 to 59,000. Blood cultures taken on Nov. 11, 16, and 25 were positive for *Escherichia coli*.

Autopsy Findings.—The autopsy was performed six hours after death. Only the pertinent findings are given. The heart weighed 335 grams. The ventricles appeared slightly dilated. The myocardium was red-brown in color and soft in consistency. A large grayish-red, rather

firm vegetation measuring 3 cm. in diameter was attached to the auricular surface of the anterior cusp of the mitral valve (Fig. 1). It practically occluded the atrioventricular orifice. It also involved both the ventricular and auricular walls adjacent to its base. The chordae tendineae of the anterior cusp were destroyed, whereas those of the posterior cusp were normal. Microscopically, the vegetation consisted of fibrin, red blood cells, polymorphonuclear leucocytes, and multiple colonies of gram-negative long and short rods and coccoidal forms (Fig. 2). The other valves were normal. The endocardium and myocardium adjacent to the vegetation were thickened and infiltrated by large numbers of polymorphonuclear leucocytes, red blood cells, and scattered mononuclear cells. The myocardium showed extensive necrosis in this region. The overlying epicardium was thickened and infiltrated by the same types of cells as were found in the myocardium. A mild diffuse scarring with scattered mononuclear cells was present throughout the remaining portions of the myocardium.

The lumina of both common iliac arteries were completely occluded by thrombi which extended from the aortic bifurcation 5 cm. distad. This did not have the characteristics of a riding embolus, but appeared to have resulted from the pelvic infection extending through the vessel walls. These thrombi consisted of fibrin, red blood cells, polymorphonuclear leucocytes, and gram-negative long and short rods and coccoidal forms. The vessel walls were thickened and diffusely infiltrated by large numbers of polymorphonuclear leucocytes and mononuclear cells.

The left pleural cavity contained 500 c.c. of straw colored fluid. The lungs were edematous, hemorrhagic, and indurated along their bases and posterior surfaces.

The peritoneal cavity contained 1,000 c.c. of a yellow, fibrinopurulent exudate. Multiple fibrous and fibrinous adhesions bound the greater omentum and intestines to the lower abdominal and plevic walls. The liver weighed 2,048 grams. It extended 5 cm. below the costal margin. The surfaces were covered with the exudate. The sinusoids were filled with red blood cells. The hepatic cells were swollen, pale staining, and granular appearing. Some showed vacuoles in their cytoplasm. There was a moderate lymphocytic infiltration about the portal triads.

The spleen weighed 340 grams. It was soft, friable, and deep red in color. Its surface was covered with the purulent exudate. The lower pole was completely necrotic. Multiple yellow infarcts containing colonies of gram-negative long and short rods and coccoidal forms were present throughout its substance.

The kidneys were soft and swollen. Their combined weight was 570 grams. The corticomedullary pattern was distorted by multiple yellow infarcts which also contained gram-negative long and short rods and coccoidal forms. Multiple petechiae were present in the mucosa of the pelves. Many glomeruli showed small areas of degeneration. The epithelial cells of the tubules showed parenchymatous degeneration. Throughout the interstitial spaces were found collections of lymphocytes and polymorphonuclear leucocytes.

The uterus was slightly enlarged and the endometrium hemorrhagic. The large blood vessels in the tunica muscularis were hypertrophied. The basilar portion of the mucosa contained numerous tortuous glands embedded in a dense cellular matrix. Large pale-staining connective tissue cells suggestive of a decidual reaction were also present in the mucosa.

The fimbriated end, including a portion of the ampulla of the right Fallopian tube, was absent. The remaining portion of this tube measured 2 cm. in diameter and was hemorrhagic. The left Fallopian tube and both ovaries were obscured by numerous dense fibrous adhesions. The fimbriated end of the left tube protruded into the pelvic cavity as a swollen, bright red, puckering mass. The wall of both Fallopian tubes were infiltrated by mononuclear cells. The right tube also showed red blood cells, polymorphonuclear leucocytes, and decidual-like cells.

The pelvic colon and the walls of the cul-de-sac were bright red in color. Two sinus tracts with indurated walls connected the lumen of the rectum with the peritoneal cavity. The entire wall of the rectum adjacent to these sinuses was diffusely infiltrated by numerous small and large mononuclear cells and polymorphonuclear leucocytes.

The brain contained numerous recent and old areas of infarction and an occasional small abscess was seen. The cerebral cortex showed marked cellular degeneration. Glial proliferation and neuronphagia were conspicuous features. The meninges were diffusely infiltrated by a moderate number of mononuclear cells,

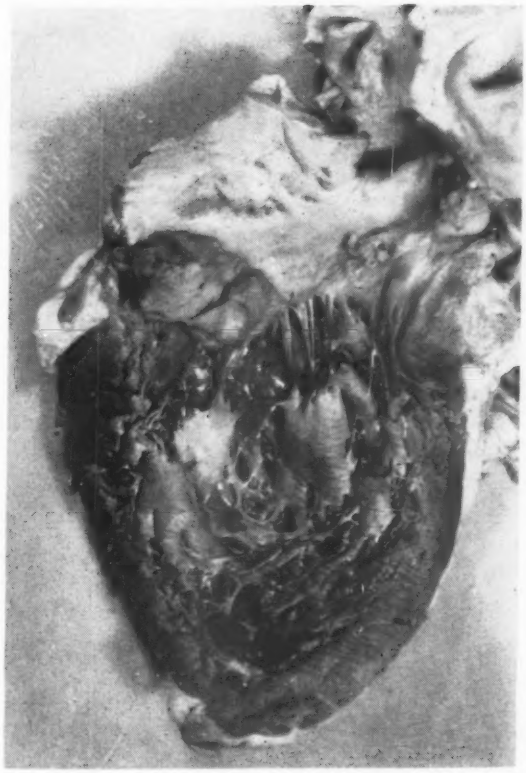


Fig. 1.—Interior of left auricle and left ventricle. A large, rather firm vegetation is attached to the auricular surface of the anterior cusp of the mitral valve.

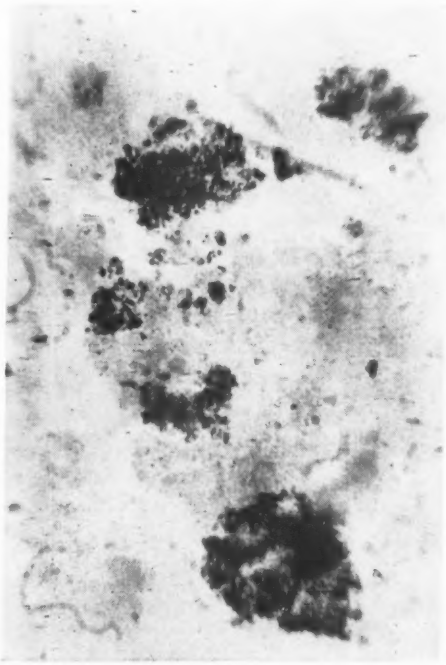


Fig. 2.—Microscopic section through vegetation. Fibrin, red blood cells, polymorphonuclear leucocytes, and colonies of gram-negative long and short rods and coccoidal forms are seen.

Pathologic Diagnosis.—(History of curettage, tubal pregnancy, and salpingectomy with drainage from abdominal incision for nine weeks.) Sinus tracts connecting the lumen of the rectum with the peritoneal cavity. Fibropurulent peritonitis. Acute arteritis with thrombi in the common iliac arteries. Acute *Escherichia coli* endocarditis of the mitral valve. Edema and hemorrhage of the lungs bilaterally; a left hydrothorax of 500 cubic centimeters. Anasarca. Multiple infected infarcts in the kidneys, spleen, and brain. Acute cystitis; chronic pyelonephritis, bilaterally. Parenchymatous degeneration of the viscera. Splenomegaly. Decubitus ulcers over the sacrum and heels.

Bacteriologic Studies.—Blood cultures taken on three occasions showed gram-negative plump rods compatible with *Escherichia coli.* These organisms formed gray colonies on agar plates and colonies having a green sheen on eosin methylene blue plates. They formed acid and gas in Russel's tube and they were methyl red positive. Multiple histologic sections through the vegetation, through the infarcts in the spleen and kidneys, and through the thrombosed iliac arteries stained by the Gram's method showed groups of gram-negative long and short rods and coccoidal forms consistent with *Escherichia coli.*

DISCUSSION

Bacillus coli endocarditis corresponds both clinically and pathologically to acute endocarditis produced by streptococcus, pneumococcus, staphylococcus, and gonococcus. The clinical onset is sudden and is accompanied by chills, rigors, high fever, and marked sepsis. The course is rapid and usually terminates fatally within six to eight weeks. It is characterized by hemorrhagic and embolic phenomena. The vegetations are large, friable, and diffusely infiltrated with organisms. Multiple septic infarcts in the spleen, kidneys and brain are the common pathologic findings.

Acute bacterial endocarditis is usually produced only by organisms of high virulence.[15] In view of the fact that the colon bacillus is considered low in pathogenic properties,[16] it is interesting that all proven cases of *Bacillus coli* endocarditis have been of the acute type. This fact suggests that either the coliform bacillus, when it becomes pathogenic for man, has its virulence greatly increased or that an organism of low virulence may produce acute endocarditis. Furthermore, the type of vegetation which is formed on the heart valve by the colon bacillus is a proliferative growth and not the ulcerative lesion usually found in acute bacterial endocarditis. The pathologic findings in the heart, therefore, resemble those seen in subacute bacterial endocarditis. This clinicopathologic discrepancy is of considerable interest.

Is the coliform bacillus capable of attacking an uninjured valve? This question is not discussed in the literature. It is generally believed, however, that only pathogenic organisms of high virulence will do this.[15] In the present case there was no pathologic evidence to suggest previous damage to either the heart or its valves. Gram stains of the vegetation showed organisms morphologically compatible only with those cultured from the blood stream, which bacteriologic studies proved to be *Escherichia coli.* Furthermore, there was no suggestion of previous cardiac involvement in the clinical history. These facts suggest that *Escherichia coli* may attack and damage a healthy valve. It is also further evident that this organism may become virulent for man.

The mitral valve appears to be the valve most frequently involved in *Bacillus coli* endocarditis. Among the twelve cases reported which designate the valve involved, the mitral valve is implicated nine times, the aortic five times, and the tricuspid valve three times. The pulmonary valve has never been involved. Table I summarizes these data.

Although *Bacillus coli* septicemia is frequent, endocarditis as a sequel rarely occurs. However, when endocarditis does occur it usually follows some operative procedure.[3] This fact is significant in the pathogenesis of this lesion. It is believed that the colon bacillus seldom passes through a healthy bowel wall. However, it has been shown experimentally that once the intestine is injured by either disease or trauma and a focus of infection established, a highly virulent strain of these organisms may develop.[17] These bacilli may be capable of producing acute endocarditis should they enter the blood stream.

It is suggested that in the present case the wall of the rectum was injured during the operation for removal of the tubal pregnancy. Necrosis, ulceration, perforation, and peritonitis followed. The infection in the peritoneal cavity produced a virulent strain of *Escherichia coli* which invaded the blood stream. The marked sepsis, damage to the mitral valve, and development of the vegetation resulted. The valvular insufficiency thus produced gave rise to the murmurs which were heard for the first time six days after the patient entered the hospital. Two months expired between the time of the operation and the onset of the marked septicemia. During this interval the patient was bedfast and ample time was provided for necrosis and perforation of the rectum and the development of peritonitis. Sixteen days elapsed between the onset of septicemia and the appearance of the mitral murmur. This is the actual time required for the endocarditis to develop to the point where it could be clinically recognized. The remaining ten days until death were marked by infarction and hemorrhagic phenomena.

SUMMARY

The literature pertaining to *Bacillus coli* endocarditis is reviewed, summarized, and evaluated. An additional case is reported. The clinical manifestations of *Bacillus coli* endocarditis are those of an acute bacterial endocarditis. The vegetation produced on the heart valve is a proliferative rather than an ulcerative lesion. In this respect it resembles the lesion usually found in subacute bacterial endocarditis. It is significant that *Bacillus coli* endocarditis usually occurs as a postoperative complication rather than as a primary disease process. It is suggested that the coliform bacillus may attack a normal valve. The probable pathogenesis of the lesion in the present case is discussed and the clinical and pathologic findings are correlated.

REFERENCES

1. Harries, G. E., and Burtenshaw, J. M. L.: Acute Infective Endocarditis Due to Bacterium Coli, Lancet **2**:803, 1937.
2. Horder, T. J.: Infective Endocarditis With an Analysis of 150 Cases and With Special Reference to the Chronic Form of the Disease, Quart. J. Med. **2**:289, 1908-1909.

3. Dickar, L.: Acute Bacterial Endocarditis Due to Bacterium Acidi Lactici, Arch. Int. Med. **49**:788, 1932.
4. Duhig, I. V.: Septicemia and Acute Infective Endocarditis Due to Bacterium Coli, M. J. Australia **1**:435, 1933.
5. Crawford, A. M., and Cruickshank, R.: A Case of Infective Endocarditis Due to Bacillus Coli, Glasgow M. J. **22**:21, 1934.
6. Lenhartz, H.: Die septischen Erkrankungen, Vienna, 1903, Alfred Hölder. (After Dickar.)
7. Jacob, L.: Ueber allgemeininfektion durch Bacterium Coli Commune, Deutsches Arch. f. klin. Med. **97**:303, 1909. (After Dickar.)
8. Jockmann, G.: Ueber Endocarditis septica, Klin. Wchnschr. **49**:436, 1912. (After Dickar.)
9. Summa; quoted by Kraus, F., and Burgsch, T.: Spezille Pathologic und Therapie innerer Krank-Heiten, vol. 2, Berlin, 1913, Urban & Schwarzenberg, pp. 1164. (After Dickar.)
10. Norris, G. W.: Studies in Cardiac Pathology, Philadelphia, 1911, W. B. Saunders Company, pp. 26.
11. Thayer, W. S.: Studies in Bacterial (Infective) Endocarditis, Johns Hopkins Hospital Reports, Vol. 22, 1926.
12. Harbetz, F.: Studies ueber Endokarditis, Deutsche med. Wchnschr. **25**:121, 1899. (After Thayer.)
13. Cowan, J.: a. Acute Endocarditis; A Clinical Study, Glasgow M. J. **108**:249, 1927.
    b. Acute Endocarditis; A Clinical Study, Glasgow M. J. **108**:338, 1927.
14. Phipps, C.: Acute Bacterial Endocarditis, New England J. Med. **207**:768, 1932.
15. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, London-New York, 1941, Oxford University Press, pp. 59-76.
16. Zinsser, H., and Bayne-Jones S.: A Textbook of Bacteriology, ed. 8, New York, 1939, D. Appleton-Century Company, Inc., pp. 492.
17. Medical Research Council: A System of Bacteriology, London, 1929, His Majesty's Stationery Office, Chapter 4.

ENDOCARDIAL POCKETS OF LEFT ATRIUM

H. K. HELLERSTEIN, M.D.
CLEVELAND, OHIO

THE object of this paper is to describe multiple endocardial pockets of the left atrium in a patient with chronic rheumatic heart disease with mitral insufficiency.

LITERATURE

The subject of endocardial pockets was excellently reviewed by Saphir in 1930 and 1933.[1,2] Few additional reports have appeared in the American literature. Abbott reported the first of five known cases of pockets in the left atrium.[3] She found an endocardial pocket in the thickened left atrium of a heart which was the seat of rheumatic mitral stenosis and which had a large patent foramen ovale. The concavity of the pocket pointed toward the left pulmonary vein. The patient, a 38-year-old white woman, had rheumatic fever at the age of 14 years and for ten years preceding death had been in cardiac decompensation. In the absence of histologic details, congenital cardiac malformation cannot be excluded.

Saphir[1] reported the second case of endocardial pockets of the left atrium in a heart which was the seat of chronic rheumatic mitral valvulitis with insufficiency. The patient was 6 years of age. In an area 2 cm. above the mitral valve, the atrial endocardium contained two pockets, 3 and 5 mm. in width. They were open toward the mitral valve. The surrounding portions of endocardium were grayish-white and thickened. Saphir considered them to be primarily inflammatory in origin and to be formed secondarily by regurgitation after the insufficiency of the mitral valve had been established.

The third and fourth cases of endocardial pockets of the left atrium were also presented by Saphir.[2] Clinical data were not included in this report. The third case resembled the second morphologically. In the fourth case, the pockets of the left atrium were secondary to a perforated fossa ovalis. Examination of the heart revealed an acute verrucous and ulcerating endocarditis of the mitral valve superimposed on a healed endocarditis. In the region of the fossa ovalis there was a round opening measuring about 8 mm. in diameter, the wall of which was thickened, firm, and slightly ragged. This opening had established a communication between the left and right atria. Between this opening and the posterior leaflet of the mitral valve there was one large somewhat horseshoe-

From the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio.
Received for publication Oct. 16, 1946.

shaped pocket and two smaller ones, the openings of all of which were directed toward the perforated fossa ovalis. The perforation of the fossa ovalis was the result of a mural ulcerative endocarditis in this region. Sections of the pockets revealed simple fibrosis and hyalinization but hardly any inflammatory cells or blood pigment. Saphir considered it likely that the pockets were caused by simple mechanical irritation brought about by the columns of blood and pressure of the blood circulating through the perforated fossa ovalis. This irritation first produced circumscribed endocardial thickenings and then the pockets.

Parsonnet and collaborators[4] reported the fifth case in a 33-year-old white man with a massive left atrium secondary to rheumatic mitral insufficiency of twenty-five years' duration. The endocardium above the posterior cusp of the mitral valve was roughened and wrinkled. On the posterior wall of the left atrium there were two semilunar endocardial pockets consisting of fibrous thickening of mural endocardium with concavities pointing toward the pulmonary veins. Microscopic sections of the left atrium revealed healed and acute rheumatic auriculitis. However, no description of the endocardial pockets was presented.

CASE REPORT

L. F., a 48-year-old white woman, was admitted to Lakeside Hospital on March 14, 1946, with a chief complaint of shortness of breath. During the five months prior to admission the patient had developed progressive dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. Edema of the lower extremities first appeared in February, 1946. This was the first episode of cardiac failure. The past medical history included the development of rachitic dorsal kyphoscoliosis at the age of 7 years. There was a questionable childhood history of rheumatic fever, with a definite residual apical systolic murmur.

On admission the patient was markedly cyanotic and dyspneic. The temperature was 36.7°C.; pulse, 88; respiratory rate, 20 per minute; and blood pressure, 130/90. There were present a caput quadratum and a marked deformity of the spine, consisting of a right dorsal scoliosis and kyphosis. Râles were heard at both lung bases. The left border of cardiac dullness was 3 cm. to the left of the midclavicular line in the fifth intercostal space. The heart rate and rhythm were normal. There was a harsh, high-pitched systolic murmur and a systolic thrill elicited best at the apex. Pitting edema of both lower extremities was present. The patient did not respond to digitalis and oxygen therapy and died on the third hospital day. The clinical diagnosis was cor pulmonale secondary to kyphoscoliosis.

Autopsy (9114) revealed chronic inactive rheumatic heart disease with profound mitral insufficiency, marked kyphoscoliosis with displacement and rotation of the heart, slight bronchopneumonia, and severe chronic passive hyperemia of the lungs, liver, spleen, and other viscera.

Eleven separate endocardial pockets were situated on the posterior wall of the left atrium (Fig. 1); ten were above the posterior commissure of the mitral valve and posterior mitral leaflet in an area 2.8 by 2.8 cm., and one was 0.6 cm. above the anterior commissure. One pocket rested partly on the interatrial septum at the inferior border of the fossa ovalis. The outline of the pockets was concave, with the concavity directed toward the apex of the heart. The pockets varied in depth from 0.2 to 0.5 cm. and from 0.5 to 1.8 cm. in their long axis, which was directed transversely, that is, roughly parallel to the valve ring. The projections forming the walls of the pockets were firm and gray. Their outer aspect was nodular, opaque, and finely wrinkled. The endocardium of the left atrium was thickened and its surface was wrinkled, dull, and opaque.

The heart weighed 329 grams. There was slight cor pulmonale and persistent ligamentum arteriosum. The pulmonic, aortic, and tricuspid valves were slightly thickened and opaque without fusion or shortening of the leaflets. The mitral valve was markedly thickened, opaque, and vascularized, particularly at the base of the leaflets. At the line of closure there were nu-

merous lamblian excrescences. There were thickening, retraction, and adhesions of the chordae tendineae. The anterior and posterior papillary muscles were hypertrophic and exhibited fibrosis of the tips.

Microscopic sections obtained according to the method of Gross, Antopol, and Sacks[5] were stained with hematoxylin and eosin. In addition, serial sections of two pockets were made. Alternate fifth sections were stained for elastic and connective tissue with hematoxylin and eosin, and by the combined Weigert and van Gieson methods (Figs. 2 and 3).

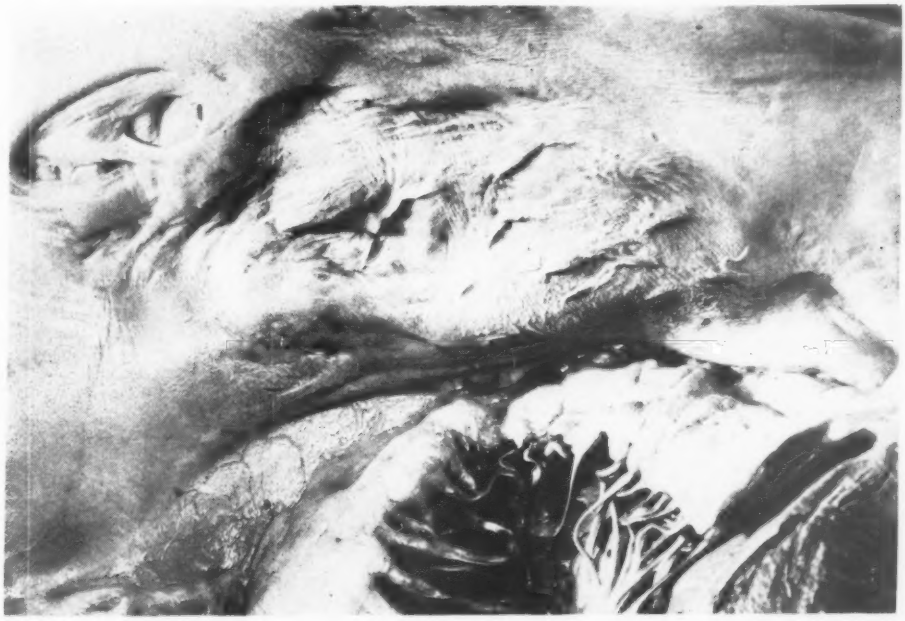


Fig. 1.—Endocardial pockets on posterior wall of left atrium. Thickening and retraction of chordae tendineae; vascularity of base of anterior mitral leaflet in lower left corner.

The endocardial pockets were orderly arranged masses of smooth muscle cells and elastic and collagenous tissue. The whole pocket appeared to arise from the superficial portion of the endocardium; that is, from a subendothelial location. There was reduplication of the elastic fibers above and below the pockets and extension of the elastic lamellae from the endocardium into the pockets (Fig. 2). They split into laminae on both the inner and outer surfaces of the pockets and formed an elastic network for smooth muscle cells and collagenous tissue in the substance of the pockets. There was slight whorling of the elastic fibers at the tip; that is, the distal outermost part of the projection (Fig. 3). The smooth muscle fibers were oriented transversely and fanned out from the lateral attachments so that in the middle two-thirds of the pockets they extended from the free border to the line of attachment. On section, the fibers presented a honeycombed appearance with centrally placed nuclei and vacuolated or clear cytoplasm (Fig. 3). The muscle cells occurred usually as compact groups or bundles and occasionally as discrete fibers. In the vicinity, or at the border, of the muscle cells there was an irregular delicate network of elastic fibers, most of which surrounded the muscle cells. The dense, sparsely cellular collagenous connective tissue was disposed in transverse bundles at the base, and longitudinally in less well-marked bundles in the free portion. The base of the pocket was partly filled with collagen. There was no vascularity, cellular exudate, or pigmentation of the endocardial pockets or the surrounding region.

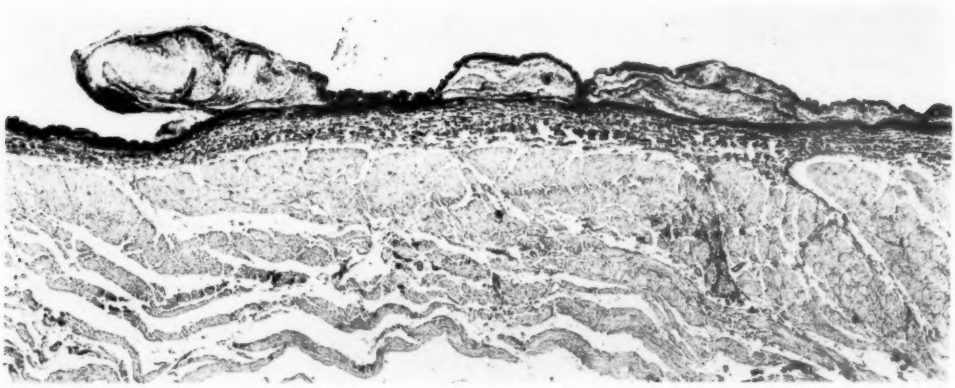


Fig. 2.—(Autopsy 9114). Endocardial pocket of left atrium and endocardial reduplications (Weigert and van Gieson × 30).

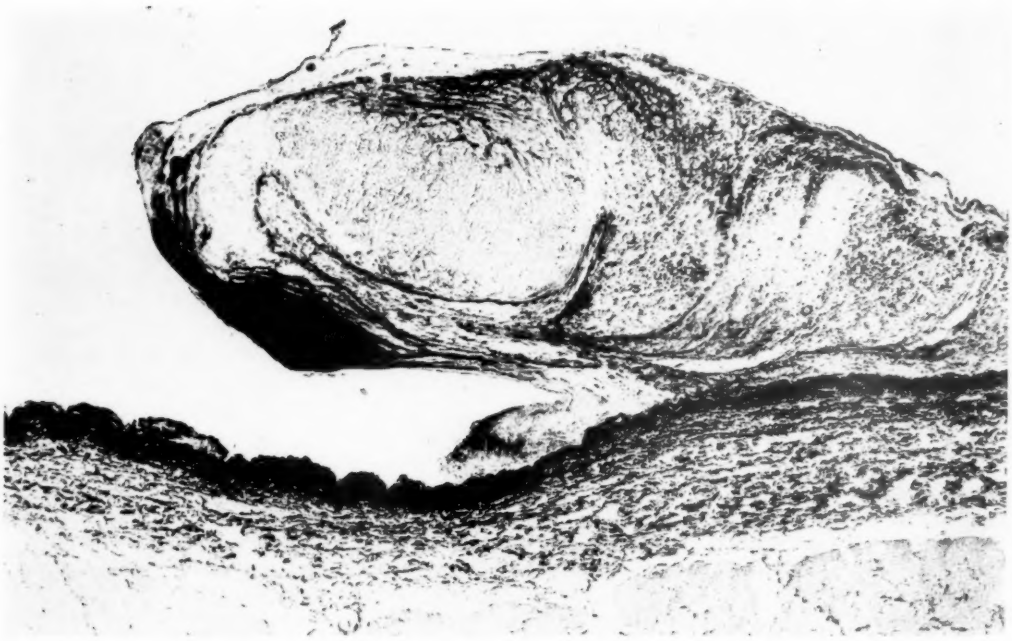


Fig. 3.—(Autopsy 9114). Higher magnification of endocardial pocket. Whorling of elastic fibers at the tip; honeycombed appearance of transverse smooth muscle fibers (Weigert and van Giesen × 117).

The mitral valve showed fibrous thickening with endocardial reduplications extending from the base to the line of closure. These were well vascularized with numerous capillaries and musculoelastic blood vessels and contained bundles of smooth muscle cells and occasionally foci of lymphocytes and plasma cells in the auricularis layer. The aortic and pulmonic valves were similarly but less severely involved. The endocardium of the left atrium was widened by numerous subendothelial plaques (endocardial reduplications) consisting of papillary masses of loosely arranged bundles of collagenous connective tissue and coarse bundles of elastic fibers. There were marked hypertrophy of the smooth muscle cells in the outer portion of the endocardium proper and irregular patchy and diffuse fibrosis of the endocardium. No Aschoff bodies were found.

DISCUSSION

Reported cases of endocardial pockets of the left atrium are rare.[1-4] Endocardial pockets of the left ventricle as a coincidental finding in cases of insufficiency of the aortic valve are relatively frequent in our experience and in that of others.[1,2,6] Saphir reported one case of endocardial pockets in the right ventricle.[2] There was a perforation of the interventricular septum, and beneath the perforation, in the right ventricle, there was an endocardial pocket, the opening of which was directed toward the perforation. In the periphery of the pocket, several small areas of endocardial thickening could be distinguished. The perforation of the septum was probably the result of an old ulcerative mural endocarditis. Saphir considered this pocket to be an anatomic witness of the interchange of blood between the ventricles. No sections were taken from this pocket. Review of the literature revealed no cases of endocardial pockets of the right atrium.

Valvular deformity has been present in every reported case of endocardial pockets. The nomenclature proposed by Krasso[7] designated diastolic pockets as those which opened toward the aorta and systolic pockets as those which opened toward the apex. Diastolic pockets were found in cases of aortic insufficiency and systolic pockets in cases of aortic stenosis and of mitral insuffiency. The pockets secondary to aortic valvular disease were located on the interventricular septum from 0.5 to 5.0 cm. below the aortic ring. The pockets of the left atrium were located from 2.0 to 3.0 cm. above the posterior mitral leaflet and in the region of the interatrial septum.

The endocardial pockets consisted of thickened endocardial folds and usually had a semilunar contour. They were composed of smooth muscle cells and elastic and collagenous tissue in orderly arrangement and arose from the superficial portion of the endocardium. Elastic lamellae extended form the endocardium into the pockets. No inflammatory reaction was present. The morphology of the left atrial pockets in the present case is similar to that described by Saphir[1] in his Cases 3 and 4, that is, systolic and diastolic endocardial pockets of the left ventricle in hearts with syphilitic involvement of the aortic valve. In Ingham and Henthorne's[6] three cases of endocardial pockets of the left ventricle, resulting from subacute bacterial endocarditis superimposed on old rheumatic endocarditis, chronic rheumatic endocarditis, and calcareous aortic stenosis, respectively, the elastic tissue similarly formed laminae on both the inner and outer surface of the pockets and also provided a fine elastic meshwork for

the connective tissue structure. In one case bundles of normal heart muscle extended into the base of the pocket in a manner similar to the extension of muscle into the tricuspid valves of normal infants. Smooth muscle cells were not found in the pockets of any of the reported cases.

Three theories have been proposed to explain the origin of atrial and ventricular endocardial pockets: (1) purely mechanical, (2) primarily inflammatory and secondarily mechanical, and (3) congenital malformation. The chronic prolonged irritation of regurgitating blood is believed to result in simple circumscribed endocardial thickenings and endocardial pockets. Exemplary cases are those of syphilitic aortic valvular insufficiency in which there are endocardial pockets on the septal surface of the left ventricle with complete absence of local inflammatory reaction. Evidence for an inflammatory basis consists of the presence of small blood vessels, remnants of blood pigment, and inflammatory cells at the line of attachment of the pockets to the endocardium and occasionally extending into the pockets. In every such case, there was a coexistent valvular defect. The pockets are then formed secondarily by mechanical excavation of the regurgitating stream of blood. The possibility that the pockets are congenital anomalies cannot be excluded with certainty, although in every reported case there has been an associated valvular lesion, either rheumatic or syphilitic. Ingham and Henthorne[6] state that there may be congenital folds of endocardium which require only the hemohydraulic factor of regurgitation resulting from insufficiency of the valves to form the pockets.

In the present case, endocardial pockets occurred in a heart which showed the stigmas of chronic rheumatic disease, that is, vascularization of the valves with thick-walled arteries, endocardial reduplication, and fibrosis of the valves and of the left atrial endocardium. The mitral valve was insufficient. In the absence of inflammation demonstrated by serial sectioning, it is logical to assume that the endocardial pockets were formed mechanically by the regurgitating blood stream. The endocardium in the region of the pockets was the seat of endocardial reduplication and thickening in this and other cases. The left atrial endocardial reduplications may be inflammatory or mechanical in origin. Endocardial reduplication, endocardial fibrosis, and hypertrophy of smooth muscle are suggestive of rheumatic disease. The absence of pathognomonic stigmas of rheumatic endocarditis (vascular penetration, cellular exudate, musculoelastic arteries, and Aschoff nodules) in the left atrium of the present case is not incompatible with an inflammatory origin of the endocardial reduplications. These stigmas in the left atrium may be absent in proved cases of rheumatic heart disease with mitral deformity.[8]

The possibility of a mechanical origin of endocardial reduplication and thickening of the left atrium of our case is suggested by the presence of similar noninflammatory lesions in localized regions of the interventricular septum subjacent to diseased aortic valves and by the absence of such lesions in cases without aortic valvular involvement.

Regardless of the origin of endocardial reduplication, in the final analysis the pockets are formed by the action of regurgitating blood which probably mechanically excavates the reduplicated endocardium with proliferation and

elastic transformation of connective tissue and metaplasia of subendothelial mesenchymal tissue into smooth muscle which later undergoes hypertrophy.

In this case and the cases reported by Parsonnet and co-workers[4] and by Abbott[3] the mitral lesion had existed forty-one, twenty-five, and twenty-four years, respectively. The significance of long duration of mitral insufficiency is problematic in view of the relative infrequency of pockets in long-standing cases of valvular heart disease. Furthermore, the patient reported by Saphir was only 6 years old. The chest deformity of our patient with rotation and displacement of the heart conceivably may have altered the dynamics of a regurgitating valve. This may have resulted in further traumatization of the posterior atrial endocardium and may have aided in the production of the lesions.

Saphir[1] believes that endocardial pockets cannot be regarded as manifestations of functional adaptation. In order for endocardial pockets to function effectively as valves, it would be necessary that the pockets be larger and sufficiently close to appose each other. The capacity of the pockets is small and probably of no functional importance. The significance of endocardial pockets, other than being a coincidental finding, is to indicate anatomic incompetence of a valve.

SUMMARY

A case which exhibited eleven endocardial pockets of the left atrium secondary to chronic rheumatic mitral insufficiency is presented.

The endocardial pockets consisted of thickened endocardial folds which usually had a semilunar contour. The concavity of the pockets was directed toward the apex of the heart. The pockets were composed of masses of smooth muscle cells and elastic and collagenous tissue in orderly arrangement and arose from the superficial portion of the endocardium. There was no vascularity, cellular exudate, or pigmentation of the endocardial pockets or surrounding endocardium.

Prolonged regurgitation of blood and the resulting pressure are the most significant factors in the development of endocardial pockets.

I am indebted to Dr. Howard T. Karsner and Dr. Simon Koletsky for their assistance in the preparation of the manuscript.

REFERENCES

1. Saphir, O.: Endocardial Pockets, Am. J. Path. **6**:733, 1930.
2. Saphir, O.: Anatomic Evidence of Functional Disorders of the Heart, Arch. Path. **16**: 315, 1933.
3. Abbott, M. E.: Two Cases of Widely Patent Foramen Ovale, Internat. Assoc. Med. Mus. Bull., Wash. **5**:129, 1915.
4. Parsonnet, A. E., Bernstein, A., and Martland, H. S.: Massive Left Auricle With Special Reference to Its Etiology and Mechanism. Report of a Case, AM. HEART J. **31**:438, 1946.
5. Gross, L., Antopol, W., and Sacks, B.: A Standardized Procedure Suggested for Microscopic Studies on the Heart With Observations on Rheumatic Hearts, Arch. Path. **10**:840, 1930.
6. Ingham, D. W., and Henthorne, J. C.: Endocardial Pockets, Arch. Path. **25**:250, 1938.
7. Krasso, H.: a. Ueber atypische endocardiale Taschenbildungen bei Aorteninsuffizienz, Frankfurt, Ztschr. f. Path. **32**:173, 1925.
   b. Die pseudovalvulären Bildungen des parietalen Endokards bei Aortenklappenfehlern und ihre Bedeutung, Frankfurt. Ztschr. f. Path. **37**:136, 1929.
8. Koletsky, S.: Microscopic Lesions of the Left Atrial Endocardium in Chronic Rheumatic Heart Disease, AM. HEART J. **29**:739, 1945.

Abstracts and Reviews

Selected Abstracts

Pruche, A.: Electrocardiograms Obtained From Precordial Positions Defined by X-rays. Arch. d. mal. du coeur **39**:323 (Oct.), 1946.

A system of bipolar precordial leads very similar to that introduced twenty years ago in Germany by Ackerman and associates is reintroduced (no reference is made to previous work). Under fluoroscopic control the beginning of the ascending aorta, the point of opposite pulsation, and the cardiac apex are marked on the chest. Electrocardiographic leads are recorded in a triangular fashion from these three points, similar to the method used for the recording of standard bipolar limb leads. A number of normal and abnormal patterns obtained by this method are presented and discussed.

HECHT.

Lian, C., and Minot, G.: Radio-Electrokymography. Arch. d. mal. du coeur **39**:339 (Oct.), 1946.

The authors describe a technique by which the pulsations of the heart and great vessels may be transformed and amplified by a photoelectric cell which is mounted on a fluoroscopic screen. The pulsations may be recorded simultaneously with an electrocardiogram on sensitized paper. Four examples of pulsations of the left ventricular border and two of expansile pulsations of the aorta are presented. Beginning and ending of cardiac ejection thus may be clearly defined. An example of aortic insufficiency demonstrates abnormal pulsations of the left ventricle and illustrates the difficulties one might have in defining the onset of systole in this valvular defect.

The technique appears similar to, if not identical with, that described by Henny and Boone in this country (Electrokymograph for Recording Heart Motion Utilizing the Reontgenoscope. Am. J. Roentgenol. **54**:217 (Sept.), 1945).

HECHT.

Marchal, M.: The Registration of Pulsations of the Lung Parenchyma and the Cardiovascular System by Kine-Densigraphy. Arch. d. mal. du coeur **39**:345 (Oct.), 1946.

Another method of obtaining electrokymograms is described which appears similar to that reported by Henny and Boone, and by Lian and Minot. Records are obtained from the right and left ventricular borders, pulmonary artery, aorta, and auricles. By placing the photoelectric cell over the pulmonary parenchyma, records may be obtained of the otherwise invisible pulsations of the pulmonary capillaries, veins, and arteries. The method may be of value in detecting stasis or alteration in flow within the pulmonary circulatory system.

HECHT.

Anrep, G. V., Barsoum, G. S., Kenawy, and Misrahy, G.: Ammi Visnaga in the Treatment of the Anginal Syndrome. Brit. Heart J. **8**:171 (Oct.), 1946.

The authors report the results of their investigation of the action of khellin on the cardiovascular system with special reference to its effect on the coronary circulation and the heart muscle, and its action in patients suffering from angina pectoris and coronary thrombosis. Experiments were made on dogs, using both the heart-lung preparation and the intact animal.

The minimal active concentration of khellin in the heart-lung preparation is about 1 in 2,000,000. With concentrations of the order of 1 in 2,000,000 the coronary blood flow increases three to four times the initial volume. The action of khellin is less than that of amyl nitrite, but it has the advantage of being much more prolonged. Gradual administration of doses as high as 100 mg. causes no change in the heart volume. Doses many times greater than those causing a conspicuous coronary vasodilatation have no injurious effects on the heart muscle. Electrocardiograms taken before and after administration of khellin were found to be identical in all respects. The pulmonary blood pressure and the rate of the denervated heart were not affected. Intravenous injections of khellin produced a temporary fall in the blood pressure, but this occurred only on rapid administration of large doses. Immediately after a rapid injection of 20 to 30 mg., the blood pressure drops to about 50 mm. Hg, the heart beats considerably slower, and the respiration is momentarily arrested. The effect lasts for only a short time. Slow intravenous injections at the rate of 2 mg. in 20 to 30 seconds can be continued for a long time without ill effects. Doses of 40 to 50 mg. per kilogram cause a prolonged fall of the general blood pressure due to peripheral vasodilatation, mainly of the splanchnic area. Khellin exerts no stimulating effect on the sympathetic nervous system. The apparently selective action of khellin in ordinary dosage on the coronary blood vessels is due to their much greater sensitivity to the drug as compared with the systemic blood vessels.

Khellin was given to forty-six patients, of whom thirty-eight had angina pectoris on effort or at rest and eight had coronary thrombosis. The duration of anginal symptoms was 3 to 12 years in fourteen cases, 1 to 2 years in seventeen, and less than a year in seven. Abnormal electrocardiograms were recorded in seventeen patients, and enlargement of the heart and aorta was found in four patients. As a control, injections free from khellin or containing a much reduced dose were substituted. Doses of 10 to 30 mg. per day by injection were found to be ineffective. A dose of 60 mg. per day gave encouraging results; and 90 to 120 mg. a day yielded better results. Single doses of 150 to 200 mg. were given without ill effect. An average effective dose proved to be 90 mg. a day. The injections caused slight and transient local pain. The average oral dose used was 40 mg. three times daily. The response to khellin was classed as good when the anginal attacks ceased altogether or became very infrequent and mild, as moderate when they diminished in frequency and severity, and negative when no change in the character of the pain occurred. Twenty-eight patients gave a good response, seven patients gave a moderate response, and three gave a negative response.

Khellin was given orally or by injection in doses of 90 to 120 mg. daily for two to five weeks after the onset of coronary thrombosis in eight patients, in six of whom there were recurrent anginal attacks during the period of recumbency. It was well tolerated and, as far as could be judged, relieved the spasmodic anginal attacks that followed the initial attack of pain.

BELLET.

Campbell, M.: Dissecting Aneurysm With Survival for Three Months After Rupture Into the Pleura. Brit. Heart J. **8**:200 (Oct.), 1946.

The author reports a case of dissecting aneurysm in which the patient survived for three months after a considerable amount of blood had ruptured into the pleural cavity.

A woman was admitted to the hospital with the history of very severe chest pain followed by collapse. The blood pressure on admission was 120/100 but soon rose to 220/130 and remained at this level after the first two days. She was found to have a left-sided pleural effusion. Aspiration one week later yielded almost pure blood. Her hemoglobin had fallen to 55 per cent and there was a leucocytosis of 15,000 with a normal differential count. The electrocardiogram showed slight inversion of T_1 and there was no significant change in the tracing a week later. At the end of two months she was allowed to be out of bed. After another month she collapsed, became unconscious, and died.

Post-mortem examination revealed that in the arch of the aorta there was a recent tear, with an escape of blood into the lung and pleural cavity. Nine centimeters below the fatal tear, there was an old transverse tear 1.5 cm. long. The dissection extended below this and the stratified clot at this point looked at least as old as, and probably older than, the clot at any other site.

It was not certain if this was the point of re-entry, or if it was the original tear causing the dissection that had spread upward and had ruptured into the lungs and the pleura near the point where the final tear had caused death.

BELLET.

Nissim, J. A.: Dissecting Aneurysm of the Aorta: A New Sign. Brit. Heart J. **8**:203 (Oct.), 1946.

In a case of proven dissecting aortic aneurysm which began at a point about 4 cm. above the aortic ring, the author encountered a physical sign to which he directs attention. There was a difference in the pulsation of the right and left common carotid arteries. The pulse was reduplicated in the right artery and single in the left artery, without noticeable difference in the strength of the pulsation on the two sides. The author feels that the explanation for this sign must lie in the difference of the rate of propagation of the pulse wave throughout the lumen of the artery, and through its dissected coats where the blood was probably partly clotted. This author suggests that this sign may be observed in other patients and may occur in other arteries.

BELLET.

Ashworth, H., and Jones, A. M.: Aneurysmal Dilation of the Left Auricle With Erosion of the Spine. Brit. Heart J. **8**:207 (Oct.), 1946.

The authors present a case which is unusual because the enlarged left auricle eroded the vertebral column, produced severe pain in the right chest, and became adherent to the right chest wall, leading to systolic retraction in the right axilla.

A single woman, 38 years of age, was admitted to the Manchester Royal Infirmary because of severe pain in the right chest of four years' duration. Her health had been good until the age of 22, when she developed rheumatic fever. At the age of 36 years she was found to have severe mitral stenosis with gross cardiac enlargement and uncontrolled auricular fibrillation. The left auricle was markedly dilated. At the age of 38 years she was readmitted to the hospital because her pain had become severe and almost continuous. The pulse was completely irregular, rate 136 a minute; the blood pressure, 130/90. Two days after admission normal rhythm with a prolonged P-R interval was recorded. Attacks of regular tachycardia lasting some hours persisted until her death seven weeks later.

Necropsy revealed the finding mentioned. The bodies of the fifth, sixth, seventh, eighth, and ninth thoracic vertebra were eroded; the intervertebral discs were spared.

BELLET.

Christensen, B. C.: Studies on Hyperventilation II. Electrocardiographic Changes in Normal Man During Voluntary Hyperventilation. J. Clin. Investigation **25**:880 (Nov.), 1946.

Four normal women, 15, 17, 30, and 42 years of age, voluntarily hyperventilated for three to eight minutes. Leads I, II, and III, and in some tests, Lead IVR were recorded during the period of voluntary hyperventilation. Tabulation of data and reproduction of electrocardiograms disclose the following changes during hyperventilation with room air: (1) sinus tachycardia, (2) a slight reduction in conduction time, (3) a reduction in the Q-T interval, (4) depression of the S-T segment 3 or more mm. in two or more leads, and (5) isoelectric, diphasic, or inverted T waves in two or more leads. There were no consistent changes in the heights of the P or R waves. Ten minutes after resumption of normal respiration the electrocardiograms were normal.

Continuation of the hyperventilation in pure oxygen did not abolish the electrocardiographic changes except in one subject. Continuation of the hyperventilation in a gas mixture containing 5 per cent carbon dioxide, 20 per cent oxygen and 75 per cent nitrogen caused the electrocardiograms of all four subjects to return to normal in thirty to sixty seconds.

Two milligrams of nitroglycerin given to two subjects just prior to hyperventilation had no influence upon the occurrence of electrocardiographic changes.

Although reduced carbon dioxide tension shifts the oxygen dissociation curve to the left and makes oxygen less available to the tissues, the author calculates that the deficit can nearly be restored when the hyperventilating subject breaths pure oxygen, by virtue of the increased quantity of oxygen in simple physicial solution. Since only one subject's electrocardiographic changes reverted to normal while hyperventilating with pure oxygen, the author implies that the myocardial hypoxia of hyperventilation is not due to an inadequate supply of oxygen. Further, since nitroglycerin does not influence the electrocardiographic changes of hyperventilation, coronary vasoconstriction due to hypocapnia and alkalosis must be unimportant in causing the electrocardiographic changes. The author believes, therefore, that increased intramyocardial tension due to hypocapnia interferes with coronary blood flow.

It is suggested that the electrocardiographic changes in febrile diseases, muscular exercise, effort syndrome, and the hypoxemia test of coronary insufficiency may be influenced by hyperventilation.

FRIEDLAND.

Breda, R., and Costa, F.: Right-Sided Ectatic Aorta. Folia Card. **5**:461 (Dec. 31), 1946.

A case of right-sided aortic arch with marked dilatation of the first part of the descending aorta is described. The patient was a 55-year-old woman who complained of difficulty in swallowing, which had been present for some time, and palpitation. The signs of Oliver, an inverted sign of Cardarelli, and a severe pulsation in the right supraclavicular and suprasternal areas were present. There was dullness at the right of the sternum. The x-ray showed typical signs of a right-sided aorta, and an esophagus which, because of dilatation of the descending aorta, presented the shape of an inverted S.

LUISADA.

Sossai, A.: On a Case of Spontaneous Rupture of the Heart With Long Survival. Folia Card. **5**:511 (Dec. 31), 1946.

A case of spontaneous rupture of the heart with survival of nineteen days is described. The patient was a 47-year-old man who suddenly complained of epigastric and retrosternal pain, dyspnea, and vomiting. Fever, fainting episodes, and jaundice followed.

After ten days, the area of precordial dullness became very large and triangular in shape. At the apex, a soft, blowing systolic murmur, becoming harsh at its end, was heard. Leucocytosis, anemia, and an electrocardiogram which was not typical of infarction were found. X-ray showed pericardial effusion, and exploratory paracentesis of the pericardium revealed fluid blood.

Autopsy revealed an acute disseminated myocarditis, fibrinous pericarditis, and hemopericardium. The diagnosis, based upon the necropsy, was acute obscure myocarditis, rupture of the left ventricle, hemopericardium, and pericarditis. The long survival (nineteen days) is undoubtedly a rare occurrence. The type of murmur is analyzed in detail and may have some diagnostic importance.

LUISADA.

Govier, W. M., Yanz, N., and Grelis, M. E.: The Effect of a-Tocopherol Phosphate, Digitoxin, and Certain Compounds Related to the Latter on Cardiac Muscle Metabolism in Vitro. J. Pharmacol. & Exper. Therap. **88**:373 (Dec.), 1946.

Anoxia of the myocardium may be one of the factors involved in congestive failure. Both a-tocopherol (vitamin E) deficient muscle and cardiac muscle in congestive failure are known to have low creatine levels. This might suggest avitaminosis E in both cases. This, in turn, could lead to coenzyme I breakdown, resulting in damage to cardiac metabolism.

It was found that, in vitro, addition of digitoxin to an anaerobic, E-deficient, lactic dehydrogenase system of guinea pig heart muscle results in a marked stimulation of the system, (increased oxygen uptake and carbon dioxide production). This does not occur in normal heart muscle or in aerobic lactic enzyme systems, normal or a-tocopherol deficient.

This effect is probably due to inhibition of coenzyme I nucleotidase by digitoxin. A-tocopherol also protects coenzyme I breakdown. Ouabain, digitonin, cholesterol, estrone, and testosterone have effects similar to those of digitoxin, to a lesser degree in the case of the hormones.

The work suggests that this action of digitoxin is to preserve cozymase by inhibition of cozymase nucleotidase, thus allowing a more normal metabolism.

GODFREY.

Jokl, E., and Melzer, L.: Rheumatic Fever Following Athletic Trauma. Acta med. orient. **6**:9 (Jan.) 1947.

These authors report two cases of trauma to large joints which they believed precipitated an attack of acute rheumatic fever with involvement of the heart.

The first case is that of a boy, aged 17 years, who received a kick in the right hip while playing football. A fortnight later he became delirious and developed neck rigidity, with signs of pleurisy and pneumonia. This was followed by acute endocarditis. During the ensuing two days the patient's temperature rose to 106° F., and death occurred soon afterward. Necropsy revealed a hypertrophied left ventricle and a fresh large crumbling thrombotic mass protruding from the ventricular surface of the anterior leaflet of the mitral valve. A small ruptured aneurysm was present beneath the thrombus that was attached to the valve. The cause of death, in the opinion of the authors, was acute rheumatic fever associated with infective endocarditis.

The second case is that of a racing cyclist, aged 21 years, who fell during a training ride and sustained an injury to his left knee. On the following day the affected joint was swollen, and a few days later the other large joints became swollen accompanied by a temperature of 104° Fahrenheit. Subsequently, the patient was admitted to a hospital where a diagnosis of rheumatic fever and cardiac involvement was made. Within the following three weeks the swelling of his joints subsided, his temperature returned to normal, but his heart "remained bad." Roentgen examination revealed an enlarged heart and the electrocardiogram suggested right preponderance. After the preceding episode, the patient experienced pain in the cardiac region and dyspnea on slight exertion, and he was no longer able to continue his athletic career. There was no improvement in this patient's condition during a five-year period of observation.

BELLET.

Dreyfuss, F.: An Observation Concerning the Hands of Patients With Rheumatic Fever. Acta med. orient. **6**:12 (Jan.), 1947.

The author draws attention to the fact that individuals who present rheumatic valvular lesions, a history of rheumatic fever, or are ill with acute rheumatic fever frequently have a particular shape of hand. Their palms usually show a tendency to be long and slender, their fingers are usually rather long, somewhat pointed, and tapering. These fingers usually do not show any prominence at the level of their interphalangeal joints. The nearer the diameter of the finger is taken to its root, the larger it is. These fingers are usually straight. Corresponding to the general appearance of many of these patients, their hands are also usually pale and often remarkably flexible. Their skin is occasionally somewhat dark above the interphalangeal joints.

The author observed this type of hand in the majority of patients with rheumatic fever or rheumatic heart lesions, more frequently in females than in males. In a series of forty-five patients (ten males, and thirty-five females) who had either active rheumatic fever with and without carditis or inactive rheumatic heart disease, this type of hand was observed in thirty-seven cases (eight males and twenty-nine females, respectively). Noting such a hand in a male patient is more striking than in a female. It serves as a hint, particularly in routine examination on patients, and should lead one to look for evidence of rheumatic involvement.

The shape of fingers described also is noted frequently in normal individuals who have no history of rheumatic fever and present no rheumatic lesions. Often relatives of rheumatic fever patients possess this type of hand.

The author believes that the occurrence of this type of hand in healthy people and particularly in relatives of patients with rheumatic fever leads one to assume that these hands are a manifestation of a constitutional type disposed to rheumatic fever, and not a result of disease.

BELLET.

Davis, L., and Perret, G.: Cerebral Thromboangiitis Obliterans. Brit. J. Surg. **34**:307 (Jan.), 1947.

The authors emphasized the point brought out by a number of workers that thromboangiitis obliterans is a generalized pathologic process affecting vessels not only in the extremities but also in many other sites of the body. The paper deals with the findings observed in eleven cases in which the cerebral vessels were involved. In only three of these was there any evidence of peripheral circulatory disturbances.

The authors state that the condition is not as rare as might be expected, but that the purely cerebral form presents many diagnostic difficulties. In fact, it has been mistaken for other pathologic entities such as syphilis, juvenile arteriosclerosis, hypertension, and intracranial tumors.

In nine of the eleven reported cases an osteoplastic craniotomy was performed, and in each instance the dura mater was loose and boggy, the arachnoid was thickened and opaque, and the subarachnoid space was distended with cerebrospinal fluid. The predominating pathologic change was segmental obliteration of the distal portions of the smaller cerebral arteries and, to a lesser extent, of the smaller cerebral veins. There was an associated yellowish discoloration, softening, and atrophy of disseminated cortical areas in the field of the occluded vessels.

The findings in the involved arteries consisted of proliferation of the intimal and subintimal cells, with little or no change in the media and adventitia. Large thrombi in various stages of organization completely obliterated the lumen of the vessels. Fresh inflammatory reactions were noted in the intima of obliterated vessels in the cases which subsequently came to autopsy.

The clinical diagnosis of cerebral thromboangiitis obliterans is based on a history of long duration of transient but progressive cerebral symptoms, evidence of cerebral atrophy in pneumoencephalograms, and possible peripheral vascular changes in the eye grounds and in the extremities. Obviously, when the condition is limited to the cerebral vessels, the diagnosis is difficult to make.

ABRAMSON.

Raab, W., and Humphreys, R. J.: Drug Action Upon Myocardial Epinephrine-Sympathin Concentration and Heart Rate (Nitroglycerine, Papaverine, Priscol, Dibenamine Hydrochloride). J. Pharmacol. & Exper. Therap. **88**:64 (Jan.), 1947.

The paper deals with artificial cardiac acceleration in the cat by means of intravenous epinephrine (atropinized specimen), stimulation of the stellate and splanchnic ganglia, and intravenous acetylcholine (atropinized specimen). In the controls, cardiac acceleration and the accumulation of epinephrine-sympathin-like substances in the myocardium were measured. The same type of experimental preparations, stimulated in the same manner, were given nitroglycerine, papaverine, priscol, and dibenamine hydorchloride.

In the controls, epinephrine produced a marked rise in pulse rate, and a massive increase of 990 per cent in the amount of epinephrine-like substance in the myocardium. Stellate and splanchnic ganglia stimulation and acetylcholine injection produced a marked rise in pulse rate, but only 21 to 35 per cent increase in epinephrine-like substance in the myocardium. Nitroglycerine markedly decreased the acceleration, but only moderately affected the accumulation of epinephrine-like substance (990 per cent to 914 per cent in animals injected with epinephrine). Papaverine practically abolished cardiac acceleration and markedly diminished accumulation of epinephrine-like substance (990 per cent to 566 per cent). Priscol and dibenamine hydrochloride both showed marked slowing effects. Dibenamine hydrochloride reduced the concentration of epinephrine-like substance from 35 per cent to 7 per cent in the stellate ganglion preparations. Priscol did not greatly influence the accumulation.

The fact that all preparations had a marked effect on acceleration, but differed greatly in inhibiting the accumulation of epinephrine-like substance, suggests that the antagonistic action against adrenosympathetic cardiac stimulation differs from drug to drug.

If epinephrine accumulates in the myocardium in angina pectoris, this work suggests that the action of nitroglycerine and papaverine may be twofold: desensitization of the myocardium to epinephrine, and coronary dilatation.

GODFREY.

Castro, V. A., and Rubio, Carlos W.: Significado de Algunas Akteraciones de las Ondas T. Arch. Inst. cardiol. Mexico **16**:98 (Feb.), 1947.

The appearance of the electrocardiogram can be modified by means of carotid sinus pressure; typical T waves (notched, flat, isoelectric, diphasic) tend to become inverted, and negative T waves tend to become more deeply inverted. These changes are transitory, but when pressure is combined with massage of the carotid sinus they may last a long time, because bradycardia and hypotension may continue for thirty minutes or more.

The effect of carotid sinus pressure is opposite to that of effort. The combination of both procedures can quickly and considerably change the shape of the T waves, without appreciably modifying the QRS complex.

AUTHORS.

Rosenblueth, A., and Ramos, J. Garcia: Action of Artificial Obstacles on Experimental Flutter. Arch. Inst. cardiol. Mexico **17**:1 (Feb.), 1947.

The authors studied the conditions which favor the appearance of auricular flutter in the dog after cutting both vagi and sympathetics. The easiest way to obtain such a rhythm is to block the conduction of impulses between the openings of the two venae cavae. This can be done either by the use of cocaine or by crushing the myocardium; the following auricular flutter continues as long as the block is present.

This abnormal rhythm is not initiated in the sinoauricular node. Its rate is accelerated by stimulation of the vagus or injection of adrenaline. Additional injuries in the damaged area decrease the rate of the flutter. Flutter can be obtained only if the damaged area is surrounded by normal conducting tissue.

LUISADA.

Mendez, R.: General Concept of Digitalis Action. Arch. Inst. cardiol. Mexico **16**:83 (Feb.), 1947.

The author discusses the actions of Angelicalactone, a synthetic lactone similar to the lactonic group of digitoxin. The substance exerts a digitalis-like action on the isolated frog heart. The toxicity on cats also might indicate a similarity in its action to digitalis. However, the latter test is inadequate because it merely reveals the toxic, and not the therapeutic activity of a substance. Therefore, the drug was tested on a heart-lung preparation after heart failure had been induced by the use of nembutal. While cardiac glycosides relieve such failure, Angelicalactone fails to do so.

The author concludes that the tested substance has no useful cardiac activity, and suggests a wider use of the heart-lung preparation as a test medium for these drugs.

LUISADA.

Dry, T. J., Edwards, J. E., Maynard, A. E., Moe, A. E., and Vigran, I. M.: Mycotic Aneurysm of the Posterior Tibial Artery Complicating Subacute Bacterial Endocarditis: Antemortem Diagnosis Confirmed by Instrumental Means. Proc. Staff Meet., Mayo Clin. **22**:105 (March 19), 1947.

The authors present a case of a 40-year-old man who, a few days prior to admission to the Clinic, experienced pain in the upper part of the left calf. On admission his temperature was 102° F., and classical signs of aortic insufficiency were present. The upper portion of the left

calf was tender and swollen, with small petechiae in the surrounding area. The dorsalis pedis and posterior tibial arteries gave strong pulsations and pistol-shot sounds could be heard clearly along the entire course of all these vessels. The diagnosis of subacute bacterial endocarditis was made and the subcutaneous administration of penicillin in doses of 40,000 units every three hours was begun. This dose was doubled the next day. After the second day of therapy the pain and swelling in the left calf appeared to subside, but on the eighth hospital day the patient again experienced sudden severe pain in this region, the pain extending into the left leg and toes. The pulse in the posterior tibial artery of the left leg was completely absent. The clinical impression was that an infected embolus had lodged in one of the branches of the left posterior tibial artery, and that perforation of the vessel had occurred when the second episode of pain developed.

On the twelfth day the patient had a sudden onset of tachycardia and tachypnea, and coarse moist râles were heard over the bases of the lungs. He died suddenly on the next day.

On post-mortem examination, the heart was found to be enlarged and the leaflets of the aortic valve were ulcerated. The aortic valve showed, in addition, evidence of an ancient inflammatory process (probably rheumatic) in the form of an organized adhesion between the left and right cusps. The left posterior tibial artery contained a thrombus originating at a point 3.7 cm. below the origin of the vessel, and extending downward for a distance of 3 centimeters. At the lower level of the thrombus, the lumen of the vessel was completely occluded and the anterior wall of the vessel was slightly dilated and perforated. Through the perforation the artery communicated with a cavity measuring 3.5 cm. vertically and 2.5 cm. across.

The diagnosis of mycotic aneurysm was suspected clinically on the basis of the history, physical signs, and sound recordings of the pulse.

BELLET.

Smith, B. C., and Quimby, E. H.: The Use of Radioactive Sodium in the Study of Peripheral Vascular Disease. Ann. Surg. **125**:360 (March), 1947.

Radioactive sodium was utilized to study the circulation time in twenty-five young normal individuals and in patients with arteriosclerosis obliterans, thromboangiitis obliterans, hypertension, frostbite, and immersion foot. The material was prepared in a cyclotron by bombarding sodium metaborate with deuterons. After it was prepared for parenteral administration, it was injected into an antecubital vein and the time of arrival of the radioactive material in the foot was determined by the use of a Geiger counter.

According to the authors, the arrival of the material at an extremity and the nature of its build-up there to equilibrium between intra- and extravascular fluid give useful information regarding the arterial circulation to the limb and, in patients requiring amputation, the site at which healing can be expected.

ABRAMSON.

Priest, Walter S., Smith, Jacques M., and McGee, Charles J.: Penicillin Therapy of Subacute Bacterial Endocarditis. Arch. Int. Med. **79**:3 (March), 1947.

The authors analyze the end results of thirty-four consecutive unselected case of penicillin treatment of subacute bacterial endocarditis. After a period of one to three years after institution of treatment, twenty-two of the thirty-five are still not only alive and symptomless but have negative blood cultures.

Streptococcus viridans was the prediminant offender, but hemolytic streptococcus, nonhemolytic streptococcus, *Staphylococcus aureus*, *Staphylococcus albus*, *Streptobacillus moniliformis* and *Hemophilus para-influenzae* were also found. In twenty-seven cases a test was made for in vitro sensitivity and found to range from 0.02 to 6.0 units per cubic centimeter.

The most important single factor in the treatment was adequate dosage of penicillin, given over a period of at least four weeks. At least 500,000 units per day should be administered, preferably by intravenous drip with isotomic saline. If intravenous drip seems impractical, the authors recommend 100,000 units intramuscularly every ninety minutes. Factors which would point to the need for higher dosage (1-2 million units daily) are (1) duration of the disease for

twelve weeks or longer, (2) sensitivity in vitro of 0.1 units per c.c. or greater, and (3) lack of response to 500,000 units. It was pointed out that failure occurred in seven of ten cases when a dosage of 400,000 units per day was given.

The authors also felt that (1) limiting fluids to 800 to 900 c.c. during the waking period results in a more constant penicillin level, (2) it was preferable to increase the penicillin dosage rather than to give substances such as para-aminohippuric acid to retard the rate of renal excretion, (3) that anticoagulants were contraindicated, and (4) that the leucocyte count and sedimentation rates were just as valuable, or more so, than the blood culture in determining the activity of the disease.

HORWITZ.

Robertson, Theodore: Paracolon Bacillus Endocarditis of the Pulmonic Valve Secondary to Infected Polycystic Kidneys. Arch. Path. **43**:318 (March), 1947.

After a left nephrocystotomy in a 40-year-old white man with polycystic kidneys, a bacteremia developed which did not respond to penicillin, sulfadiazine, or blood transfusions. The patient died with uremia.

Autopsy showed two huge kidneys containing numerous cysts, mostly filled with thick foul-smelling pus. The heart weighed 400 grams and the left ventricle was hypertrophied. The pulmonic valve leaflets were almost destroyed and replaced by large vegetations composed of firm yellow granulation tissue. Many smaller vegetations were ulcerated. The other valves were normal.

The spleen weighed 550 grams, was dark red and firm. Post-mortem cultures of the heart blood, the lung, and of pus from the renal cysts were all positive for the paracolon bacillus. A crushed piece of the pulmonary valve vegetation gave a positive culture for the same organism.

It appeared that there was no chronic valvular damage preceding this vegetative endocarditis. This is the first recorded instance of paracolon endocarditis.

GOULEY.

Jones, A. B.: Peripheral Venous Thrombosis: Preventive Measures and Treatment. M. J. Australia **1**:297 (March), 1947.

The author reviewed the literature regarding the incidence of peripheral venous thrombosis and the generally accepted procedures utilized in the prevention of this condition, as well as the medical and surgical treatment. No new concepts were discussed nor was any attempt made to elaborate upon any controversial points.

ABRAMSON.

Olson, W. H., and Necholes, H.: Studies on Anuria: Effect of Infusion Fluids and Diuretics on the Anuria Resulting From Severe Burns. Surg., Gynec. & Obst., **84**:283 (March), 1947.

The authors, by means of severe burns in anesthetized dogs in acute experiments, have correlated the urinary output with the hematocrit and the degree of hemoglobinemia. They observed, along with others, that the anuria associated with severe burns, the crush syndrome, and incompatible blood transfusions are largely due to circulating free hemoglobin and myoglobin and their deleterious effects on the kidney.

In the present paper the authors focus their attention on the study of a variety of diuretics which may have clinical value in the overcoming of the anuria associated with severe burns. They found, confirming Maitland's observation in 1941, that infusions of isotonic sodium sulfate were vastly superior to any other diuretic studied and that it was the only one which would effect a good diuresis in the presence of high blood levels of hemoglobin. Plasma and saline were the least effective solutions.

LORD.

Robles Gil, J.: Clinical and Histopathological Study of the Nodules in Various Rheumatic Diseases. Arch. Inst. cardiol. México **17**:169 (April 30), 1947.

The nodules of various rheumatic diseases were studied from a clinical and histologic point of view. A comparison of the findings with similar findings reported from other countries was also made. Biopsy was done in many subjects.

The cases include 205 patients with rheumatoid arthritis, 667 with rheumatic fever, 183 with osteoarthritis, and 35 with gout. No difference was found between these nodules and those described in other countries. The clinical and histological aspects of the nodules in rheumatic fever and rheumatoid arthritis seem to show: (a) that they are different diseases; (b) that they are real pathologic entities and not syndromes caused by various agents; (c) that the nodules are similar to those observed in certain chronic infectious diseases, though different in some aspects; (d) that they are similar to lesions found in other organs of the same patients; and (e) that they are signs of activity of the process and have a definite prognostic importance.

Heberden nodes are the result of a degenerative process, similar to that observed in several joints of the same patients. Chronic trauma and circulatory and endocrine disturbances seem to play a certain role in the osteoarthritic manifestations.

Differential diagnosis is considerably helped by biopsy with histologic study of the nodules.

LUISADA.

Ortiz Ramirez, T.: Variations of Cardiac Pain Caused by Respiration, Postural Changes, and Pressure. Arch. Inst. cardiol. México **17**:224 (April 30), 1947.

Cardiac pain may be accompanied by manifestations which are commonly thought to be typical of pain due to other causes. Breathing, changes in the position of the body, and external pressure may increase cardiac pain. The author explains this fact by the theory of "referred pain." He further points out that some of the accepted methods for differentiating "cardiac pain" from "thoracic pain" have no actual value.

LUISADA.

Salazar Mellen, M., Lozano Lube, E., and Brenes, M.: A Comparative Study of Cultures of Arterial or Venous Blood and Bone Marrow in Patients With Subacute Bacterial Endocarditis. Arch. Inst. cardiol. México **17**:229 (April 30), 1947.

The authors studied 327 samples of bone marrow and arterial and venous blood from eighty-eight clinical cases, diagnosed as having subacute bacterial endocarditis. All three types of cultures were positive in twelve cases. Bone marrow cultures were positive in twenty-one cases, arterial blood cultures in fifteen, and venous blood cultures in nineteen.

The cultures made with arterial blood were never positive when the others were negative. Cultures of bone marrow were positive when blood cultures were negative, but only in patients under penicillin treatment.

In conclusion, cultures of bone marrow may be helpful where technical difficulties for arterial or venous cultures are present or in doubtful cases. Moreover, they may permit us to ascertain when a case of subacute bacterial endocarditis is cured.

LUISADA.

Krontiris, A.: Experiences With Sympathectomy for Sequelae of Trench Feet. Ann. Surg. **125**:505 (April), 1947.

Twenty-seven patients demonstrating the late sequelae of trench foot were subjected to lumbar sympathetic ganglionectomy. The immediate results consisted of alleviation of pain in the affected foot and disappearance of hyperhidrosis. The delayed results were studied with regard to ulcerations. Those lesions situated in the lower part of the leg healed rapidly and permanently, while little effect was noted in those instances in which the foot, particularly the heel, was involved. In the case of the latter, plastic repair was subsequently necessary, and this procedure in most instances was successful. However, the author was inclined to believe that the prolonged period of rest in bed, rather than the sympathectomy, was responsible for the

therapeutic results. The author concluded that sympathectomy in the treatment of the sequelae of trench feet produced a temporary reduction in pain and in the vasomotor instability, while it had a doubtful and uncertain therapeutic effect on the healing of ulcerations.

ABRAMSON.

Hufnagel, C. A.: Permanent Intubation of the Thoracic Aorta. Arch. Surg. **54**:383 (April), 1947.

The author reviews the methods of the nonsuture technique of vascular anastomosis and points out defects and limitations of each of them. For the first time, by means of highly polished lucite (methyl methacrylate) tubes, Hufnagel was able to intubate the thoracic aorta of dogs and have the tubes remain patent indefinitely. The plastic, lucite, possesses the quality of delaying coagulation of the blood due to its pronounced water-repellent surface. One important problem was overcome when the author found that miltiple braids of braided silk (U. S. P. No. 2) did not crush the wall of the aorta and held the tube satisfactorily. No clinical material was presented.

LORD.

Mylks, G. W., Brown, A. B., and Robinson, C. N.: Air Embolism During Labour. Canad. M. A. J. **35**:427 (April), 1947.

The purpose of this report is to record a case of air embolism as a complication of labor.

A white woman, 32 years of age, showed considerable edema of the feet, ankles, and legs in approximately her eighth month of pregnancy. Her weight had risen over 18 pounds in six weeks, the blood pressure was 162/94, and urine contained a heavy trace of albumin. She was admitted to the hospital and put on a high protein, low salt diet. During the ten days spent in the hospital her blood pressure fell to 122/82 and she lost 14 pounds in weight. Induction of labor was attempted, but failed. Soon thereafter labor began spontaneously.

At the onset of labor she experienced a chill, her temperature rose to 101° F., vomiting occurred, she became very restless and was cyanosed, and went into shock. The pulse at this time was 150 per minute and the systolic blood pressure was below 80 mm. Hg. She was given a blood transfusion in one arm and distilled water with 10 per cent glucose in the other. The fetal heart rate was 120 beats per minute. Oxygen inhalation was administered. The baby was stillborn and the patient died.

Autopsy, performed two hours after death, showed the first evidence of the cause of death when the vessels of the breast were cut and air bubbles could be seen escaping with the blood. When the heart was compressed and the right ventricle opened, air bubbles rushed out. On opening the chest both lungs were found collapsed.

In this case of air embolism during labor no other mode of entry for the air seems plausible except through the uterine sinuses. The authors explain that the air reached the systemic circulation because the air bubbles became so reduced in size from absorption that they were able to pass to the left side of the heart. It is noted that most reported cases of air embolism associated with labor have usually been preceded by operative interference.

BELLET.

Lupton, A. M.: The Effect of Perfusion Through the Isolated Liver on the Prothrombin Activity of Blood From Normal and Dicumarol Treated Rats. J. Pharmacol. & Exper. Therap. **89**:306 (April), 1947.

Liver from both normal rats and rats that had been given dicumarol prior to sacrifice were isolated and perfused through the portal vein. Blood was drawn from both normal and dicumarol-treated rats. The blood was citrated, perfused continuously for two hours, and tested frequently for prothrombin activity.

Normal blood perfused through the liver of normal rats showed no change in prothrombin activity. Normal blood perfused through livers of dicumarol-treated rats resulted in no change

in the prothrombin activity of the blood. Blood from dicumarol-treated rats perfused through normal livers showed a significant increase in prothrombin activity.

These results suggest that the liver is the site of prothrombin formation.

GODFREY.

Kipple, H. M., Waldman, M. S., Hall, V. E.: Cardiovascular Effects of Sodium Caprylate in the Cat. J. Pharmacol. & Exper. Therap. **89**:313 (April), 1947.

Using intact cats in the recording of venous and arterial pressure, and ventricular volume in systole and diastole (cardiometer), the results of intravenous injection of Ringer's solution were compared with those following the injection of sodium caprylate in concentrations ranging from 0.075 to 0.75 mm. per kilogram. The results of caprylate injection differed quantitatively from those of Ringer's solution. There was a temporary dilatation of the heart, an increased stroke volume, and an increased cardiac output and venous pressure. With a constant diastolic volume there is a slight increase in stroke volume with sodium caprylate as compared to Ringer's solution. The blood pressure was higher with the former than with the latter. The preceding actions suggest that sodium caprylate has some digitalis-like action on the cat heart.

GODFREY.

Dawes, G. S. L.: Studies on Veratrum Alkaloids. VII. Receptor Areas in the Coronary Arteries and Elsewhere as Revealed by the Use of Veratridine. J. Pharmacol. & Exper. Therap. **89**:325 (April), 1947.

Veratrum alkaloids are known to cause a fall in blood pressure and heart rate. Impulses for this action are believed to arise from the afferent cardiac branches of the vagi; the effect on the heart is abolished by section of the vagi.

The coronary arteries and their branches in intact cats and dogs were canalized and their circulation kept intact by means of arterial anastomosis, leaving them available for direct intra-arterial injection. Injection of veratridine into the femoral artery results in a smaller fall in blood pressure and pulse rate than when the same concentration is injected into the left ventricle. Minute amounts of drug (0.1 to 0.25 microgram) injected into the coronary arteries produces a marked fall in blood pressure and pulse rate.

Injection into branches of the coronary arteries supplying the left ventricle had a maximum effect.

Veratridine injected into the perfused left lung also causes a fall of blood pressure and heart rate; however, larger doses must be used than in the coronary circulation.

Veratridine potentiates the action of potassium chloride on the central nervous system in causing a fall in blood pressure and heart rate and reducion in depth and rate of respiration.

GODFREY.

Copley, A. L., and Stefko, P. L.: Coagulation Thrombi in Segments of Artery and Vein in Dogs and the Genesis of Thromboembolism. Surg., Gynec. & Obst. **84**:451 (April), 1947.

The purpose of the experimental study was to determine whether tissue juice from veins of homologous and heterologous origin would coagulate the stagnant blood within a formed vessel segment in vivo. The investigation was performed on dogs, using the carotid and femoral arteries and the jugular and femoral veins.

Tissue juice from veins of dogs and chickens induced coagulation thrombi in segments of arteries, while tissue juice from veins of dogs produced this response in segments of veins. Human placental thromboplastin induced coagulation thrombi in both arteries and veins. The authors found that in the absence of infection the coagulation thrombi were nonadherent to the vessel wall and exhibited clot retraction. Attention was called to the similarity of this type of thrombus to the entity of phlebothrombosis with regard to embolus formation. Physiologic saline, used as a control, did not cause coagulation thrombi nor did mechanical manipulations. Crushing of the vessel segment over silk produced the response on occasion.

The authors devoted a considerable portion of their paper to a review of the literature and a discussion of the various factors responsible for intravascular blood clotting and for the formation of thromboembolism.

ABRAMSON.

Thebaut, B. R., and Ward, C. S.: Ligation of the Inferior Vena Cava in Thrombo-Embolism. Surg., Gynec. & Obst. **84**:385 (April), 1947.

The paper deals with the controversial subject of the treatment of pulmonary embolism. The authors advocate venous ligation at high levels and, in support of their veiw, present the results obtained with ligation of the inferior vena cava in thirty-six patients suffering from pulmonary embolism having its origin in the deep veins of the lower extremities. It is the author's belief that this procedure should be used routinely under such circumstances, since it offers the patient the best prognosis for both immediate and ultimate results. They are not impressed by the therapeutic use of anticoagulants in preventing further episodes of pulmonary embolism in a patient already suffering from this condition, although they acknowledge the value of the treatment as a prophylactic measure before thrombosis has occurred or following ligation of the inferior vena cava, to prevent the thrombotic process from extending into unaffected vessels. They also express disappointment in the treatment of deep thrombosis by proximal venous ligation at levels below the common iliacs, calling attention to the fact that from personal observation and on the basis of reported cases, emboli may recur despite bilateral femoral vein ligation. Even if this procedure is combined with phlebotomy and aspiration of the thrombus, as suggested by some workers, there is still great danger in leaving even a small portion of thrombus or an area of roughened intima in the vein proximal to the site of its interruption, since such a nidus may become the source of a new propagating thrombus and pulmonary emboli.

The authors point out the technical advantage of inferior vena cava ligation, which requires only a single operation, as compared with bilateral femoral vein ligation. At the same time the procedure offers protection not only from emboli arising in the veins at both lower extremities but from a pelvic source as well. The only major disadvantage is that a spinal or general anesthetic is necessary for inferior vena caval ligation, whereas femoral vein ligation can be carried out under local anesthesia. Attention is also directed to the findings reported by several investigators that the collateral circulation following interruption of the common femoral or the external iliac vein is far less satisfactory than that following ligation of the common iliac or the inferior vena cava. Hence, it would be expected that the edema of the extremity would be less severe and of shorter duration following high ligation. This view has been borne out clinically. However, the majority of the patients in the series did have a mild degree of dependent edema in the lower extremities for several months after operation, although in none was this incapacitating. Immediately after the procedure was carried out, in more than half the cases there was a definite aggravation of symptoms in the involved extremity, particularly an increase in edema.

Four of the patients in the series died, two on the operating table, before the vena cava was ligated. One died twenty minutes after closure of the incision, and another five hours later. Two patients in the series developed increased chest pain following operation but recovered completely. X-ray studies confirmed the impression that no new areas of pulmonary infarction had occurred in these individuals.

The technique for ligation of the inferior vena cava and the postoperative care are presented in detail.

ABRAMSON.

Collins, V. J., Foster, W. L., and West, W. J.: Vasomotor Disturbances in Poliomyelitis, With Special Reference to Treatment With Paravertebral Sympathetic Block. New England J. Med. **236**:694 (May 8), 1947.

In a group of 131 patients convalescent from poliomyelitis, the authors noted the frequent occurrence of edema, hyperhidrosis, coldness, chilblains, and other manifestations of vasomotor disturbances. The severity of these manifestations did not parallel the extent of the motor paralysis. Lumbar paravertebral sympathetic block was performed on patients with lower extremity

involvement, and stellate ganglion block on those with upper extremity involvement. The technique is described.

All patients treated showed temporary improvement, subjectively and objectively. The duration of improvement increased after each subsequent block. In several cases, after the third or fourth block, the improvement was of many weeks' duration. The efficacy of this treatment in the relief of muscle spasm, tenderness, and pain was of especial interest.

KAY.

Allen, E. V.: The Clinical Use of Anticoagulants. J. A. M. A. **134**:323 (May 24), 1947.

The author discussed in detail the action of heparin and dicumarol and their clinical use in intravascular clotting. The exact dosage of the drugs and the treatment of overdosage were also presented.

On the basis of a study of a large series of cases, the author was of the opinion that dicumarol is effective in preventing venous thrombosis or in checking its extension once it has occurred. He concluded that the judicious and expert use of anticoagulants is at least as effective in counteracting pulmonary embolism as is ligation of large veins. However, he did acknowledge that in cases in which there is repeated venous thrombosis and pulmonary embolism, ligation of a vein may be superior to anticoagulant therapy because of the difficulty of administering the latter over a long period. According to the author, the danger of bleeding from the use of anticoagulants is minimal, provided their adminstration is properly controlled by repeated laboratory tests.

ABRAMSON.

Birchall, R., Taylor, R. D., Lowenstein, V. E., and Page, I. H.: Clinical Studies of the Pharmacologic Effects of Tetraethyl Ammonium Chloride in Hypertensive Persons Made in an Attempt to Select Patients Suitable for Lumbodorsal Sympathectomy and Ganglionectomy. Am. J. M. Sc. **213**:572 (May), 1947.

It was reasoned by the authors that, if tetraethyl ammonium chloride had a highly selective depressing action on sympathetic ganglia, it should be possible to estimate pharmacologically the effect on blood pressure of lumbodorsal sympathectomy and ganglionectomy; this would provide a method for selecting candidates suitable for operation. However, the results presented indicate that, in addition to its effect on the sympathetic ganglia, it affects the parasympathetic ganglia and sensory nerve fibers and impairs motor function. Mydriasis and dry mouth represent inhibition of the parasympthetic components. All of the patients studied experienced some degree of numbness and tingling immediately following injection of the drug, which suggested that it acts upon sensory nerve fibers. Its curare-like action was indicated by dysarthria, dysphagia, ptosis, and, finally, intercostal and diaphragmatic paresis.

A drug which acts so diffusely in human beings might be expected to affect the blood pressure in a manner different from that of sympathectomy and ganglionectomy. That this is true is indicated by the fact that the degree of arterial pressure reduction induced in the cases studied bore no relationship to that following the operative procedure.

The study included eleven patients with essential hypertension, four with malignant hypertension, and one with chronic Bright's disease. Fourteen of the sixteen patients had appreciable reduction of blood pressure with the drug, as well as after the sodium amytal test. Twelve of these were operated upon, but only two of them had any significant change in resting supine blood pressure measurements two to four weeks after operation.

DURANT.

Breitwieser, E. R.: Electrocardiographic Observations in Chronic Cholecystitis Before and After Surgery. Am. J. M. Sc. **213**:598 (May), 1947.

Preoperative and postoperative electrocardiographic studies in seventeen cases of calculous cholecystitis and one case of noncalculous cholecystitis are reported, all of the cases having had abnormal preoperative tracings. Including those with cardiac symptoms, as well as those with-

out, 50 per cent showed reversion of the T waves toward normal following gall bladder surgery. Exclusion of the five patients with hypertension did not significantly change this percentage. The author concludes that T-wave changes, unless associated with other indications of severe myocardial damage, should not be considered a contraindication to operation in chronic cholecystitis.

It should be added that the amount of T-wave change in the one set of tracings reproduced is very minimal.

DURANT.

Zeman, F. D., and Siegal, S.: Monoplegia Following Carotid Sinus Pressure in the Aged. Am. J. M. Sc. **213**:603 (May), 1947.

A man, aged 83 years, with long-standing hypertension, developed a permanent right monoplegia within a few minutes after carotid sinus testing in the recumbent position. A review of the literature is presented and includes the observation of others that irreversible reactions to the cerebral type of carotid sinus hypersensitivity may occur. A warning is sounded against the casual employment of carotid sinus pressure either as a diagnostic test or therapeutic measure in aged patients suffering from hypertension and arteriosclerosis. It is suggested that the hypersensitive carotid sinus reflex may play a role in the precipitation of spontaneous cerebral accidents, and it is devised that aged patients, or even those over 50, with hypertension or arteriosclerosis be warned to avoid constriction of the neck, abrupt movements of the neck or head, straining at the stool, or heavy lifting and bending.

DURANT.

Kirk, G. D.: Ligation of Inferior Vena Cava for Septic Thrombophlebitis. Am. J. Surg. **73**:606 (May), 1947.

The author presented a case of septic iliofemoral thrombophlebitis following reactivation of an old retropelvic infection associated with a gunshot wound of the right buttock and sacrum. When the infection could not be controlled by penicillin and, subsequently, by streptomycin, the inferior vena cava was ligated in an attempt to control the septicemia. Following this procedure there was moderate edema of both thighs, particularly the left, and of the back, which reached its maximal degree in the third day and subsided to practically normal by the eighth day. Despite the operation, the patient died of a suppurative meningitis.

ABRAMSON.

Shafiroff, B. J. P.: Ligation of the Inferior Vena Cava. Am. J. Surg. **73**:621 (May), 1947.

A case is reported of a 22-year-old man who developed a pulmonary embolus seven days following an appendectomy for acute appendicitis. During the next two weeks a bilateral thrombophlebitis of both legs was observed. The patient was treated with sulfadiazine and oxygen, and later with penicillin and heparin. He was discharged as recovered after three months of hospitalization.

Three months later a new pulmonary embolus occurred, and shortly thereafter a thrombophlebitis of the right leg. Examination revealed, in addition, tenderness of both femoral veins and positive Homan's signs. Ligation of the inferior vena cava was carried out along with perivenous stripping of the vena cava and excision of the right third lumbar sympathectic ganglion. The postoperative course was uneventful and during the follow-up period of seven months the patient has remained entirely well, except for a twenty-four hour period of redness and tenderness of a superficial vein of the thigh.

The author concludes that ligation of the inferior vena cava is a sound operation and is indicated when a diagnosis of pelvic vein thrombophlebitis or bilateral phlebothrombosis of the lower extremities has been made.

LORD.

Davis, E.: Mitral Stenosis and Pulmonary Tuberculosis. Am. Rev. Tuberc. **55**:457 (May), 1947.

This author reports that nearly 1 per cent of patients with active pulmonary tuberculosis had mitral stenosis. Among 725 patients with active pulmonary tuberculosis who had tubercle bacilli in their sputum, twenty-seven patients gave convincing evidence of rheumatic fever, and three others gave a history of chorea in childhood. Of the twenty-seven cases with evidence of rheumatic fever and tubercle bacilli in their sputum, six showed unequivocal signs of mitral stenosis. The remaining twenty-one patients, although they showed rheumatic mitral disease, did not have stenosis. During the period when these 725 patients with active tuberculosis were seen, 538 other patients were seen with convincing histories or signs of rheumatic fever or chorea. Of these, three developed lymphocytic pleural effusions, and three others stated that they developed active pulmonary tuberculosis from which they recovered.

BELLET.

Morton, J. J., Mahoney, E. B., and Mider, G. B.: An Evaluation of Pulmonary Embolism Following Intravascular Venous Thrombosis. Ann. Surg. **125**:590 (May), 1947.

Morton and associates analyze their experience over the past twenty years at the Strong Memorial and Rochester Municipal Hospitals with venous thrombosis and pulmonary embolism. They found that most fatal emboli occur in surgical patients over 50 years of age and that there was no significant sex difference. One important factor in determining whether an embolus would prove to be fatal was the state of the heart. Patients with impaired circulation due to weakness of the cardiac muscle, valvular defect, and congestive failure were more susceptible to fatal embolization. The vast majority (80 per cent) of emboli occurred during the first two postoperative weeks.

The authors point out the position patients assume in bed and the degree of muscular activity while in bed are important in preventing venous thrombosis. The so-called "jack-knife" position impairs the venous return, whereas a relatively straight bed avoids this difficulty. Active exercises in bed are valuable, and early ambulation, when walking is practiced, is useful.

LORD.

Craig, W. M., and Abbott, K. H.: Surgical Considerations in the Treatment of Hypertension. Ann. Surg. **125**:608 (May), 1947.

Hypertension is classified as (1) secondary, due to nephritis, urinary obstruction, and coarctation of the aorta, and (2) essential, or primary. The authors then grade hypertensive patients into four groups, employing Keith, Wagener, and Barker's definitions. From an analysis of their experience at the Mayo Clinic, Groups 1 and 2 (mild and moderate) are favorable for surgical intervention, whereas patients with advanced and fixed hypertension are less suitable.

The authors discuss briefly the various types of operations suggested for the lowering of the blood pressure and conclude that each one may be useful and have its place. The greatest problem remaining is the development of a test, or series of tests, for the selection of cases for surgical therapy.

LORD.

Walton, R. P., and Brodie, O. J.: The Effect of Drugs on the Contractile Force of a Section of the Right Ventricle Under Conditions of an Intact Circulation. Measurement of Isometric Systolic Tension By Means of Calibrated Springs Attached to Myo-Cardiograph Levers. J. Pharmacol. & Exper. Therap. **90**:26 (May), 1947.

Small sutures were placed in the myocardium of the exposed right ventricle of dogs. These sutures were then connected with a calibrated myograph so arranged that a known force could be excited in the direction opposite to systole. Control figures for the amount of force necessary to abolish excursions of the recording lever during systole were first obtained on each specimen. Various drugs were administered in known quantities and the force necessary to abolish the sys-

tolic excursion noted. The results were expressed in percentage increase and decrease compared to the initial control.

Digitalis caused a consistant increase in isometric contraction, averaging plus 37 per cent to plus 170 per cent. Epinephrine, likewise, showed a consistant increase, averaging plus 225 per cent. Ephedrine, both in very small repeated doses and in single large doses, caused a consistant increase. With repeated massive single doses there was a decrease in isometric contraction with cardiac dilatation.

EA-83 (2-methylamino-6-hydroxy-6-methyl heptane) produced a consistant increase in strength of contraction, but blood pressure was not as markedly elevated as it was with epinephrine. Caffeine barium, calcium, and potassium salts all produced an increase in isometric contraction; quinidine and amyl nitrite produced a decrease.

The study of isometric systolic tensions may furnish a method of bioassay for cardiac drugs.

GODFREY.

Elkeles, A.: Disseminated Ossified Nodules in the Lungs Associated With Mitral Stenosis. Proc. Roy. Soc. Med. **40**:405 (May), 1947.

The author describes a special type of pulmonary nodular calcification occasionally encountered in patients with mitral stenosis. He suggests that the ossified pulmonary nodules are the end result of rheumatic pneumonia and not, as hitherto believed, the outcome of long-standing passive congestion of the lungs in mitral stenosis.

Two cases of rheumatic heart disease with advanced mitral stenosis are reported which presented such calcifications. One of these came to necropsy. Microscopic examination of the nodules proved them to consist of bone of the woven type and intra-alveolar in position. The healed primary focus of tuberculosis can be distinguished from the ossified nodules in mitral stenosis by the destruction of the elastic framework of the affected area and by marginal calcification.

The author compares the radiologic appearance of pulmonary lesions of calcified miliary tuberculosis with those of the calcified nodules in mitral stenosis. In mitral stenosis the calcified nodules vary in size from pinhead to a large pea. They show various shades of density, are not always discrete, and have a tendency to coalesce. The nodules are distributed over the central lung fields, as well as the periphery. In calcified miliary tuberculosis the calcified nodules are discrete and more uniform in size and density. They mainly involve the central lung fields. There is usually evidence of primary or of post-primary tuberculosis lesions.

BELLET.

Eichna, L. W., Horvath, S. M., and Bean, W. B.: Post-exertional Orthostatic Hypotension. Am. J. M. Sc. **213**:641 (June), 1947.

Transitory nonfatal collapse following severe physical effort is a familiar phenomenon in competitive sport. Observations dealing with the orthostatic hypotension, which is one of the circulatory aspects of this "Sportkrankheit," have been few, however. While studying the physiologic effects induced in healthy young men worked to the limits of their physical tolerance, the authors encountered postexertional orthostatic hypotension and had an opportunity to study it.

It was found that orthostatic hypotension developed in approximately one-half of the subjects following vigorous exercise of the lower extremities. It followed prolonged moderate work, as well as acute exhausting effort. In one-half of those who developed orthostatic hypotension (one-fourth of all subjects) the hypotension was so severe that syncope resulted. There was often a persistence of the orthostatic hypotension for periods longer than one hour after cessation of the inducing physical effort. The causative factor appeared to be a pooling of blood in the dependent lower extremities, presumably due to failure of the muscular venopressor mechanism in the legs, plus a work-induced dilatation of their vascular beds. During the orthostatic hypotension, maneuvers which move blood out of the lower extremities, or exclude blood from them, relieve the hypotension.

DURANT.

Odell, L. D.: Renal Filtration Rates in Pregnancy Toxemia; Inulin and Exogenous Creatinine. Am. J. M. Sc. **213**:709 (June), 1947.

Simultaneous inulin, exogenous creatinine, and urea clearance tests were obtained from fifteen women, twelve of whom had severe signs of pregnancy toxemia. Urinary output, under identical conditions of fluid intake, improved markedly post partum. Results for urea clearance compared favorably with established standards. With few exceptions, figures for exogenous creatinine clearance exceeded those for inulin.

In severe pre-eclampsia, inulin, exogenous creatinine, and urea clearance rates were comparatively reduced ante partum, and improved during the puerperium. Considerable variation in inulin clearance values exists in patients with pregnancy toxemia.

Severe cases, particularly those with oliguria, cannot be accurately investigated by the usual methods employing collected urine specimens. Consequently, additional evidence is necessary to determine the exact mechanism of oliguria and anuria. The possible etiological significance of angiospasm is postulated, since transient oliguria has been produced experimentally by prolonged immersion of a limb in an ice water bath, and, in addition, arteriolar constriction has been detected by ophthalmoscopy during an ice water test.

DURANT.

Poppen, J. L.: Extensive Combined Thoracolumbar Sympathectomy in Hypertension. Surg., Gynec. & Obst. **84**:117 (June), 1947.

Poppen describes a technique for the removal of the sympathectic chain from the fourth thoracic through the second lumbar ganglia, along with the great, lesser, and least splanchnic nerves. Exposure is obtained extrapleurally by resection of short medial segments of the seventh or eighth ribs and the eleventh rib. The pleura has been accidentally opened in five per cent of the operations. Every effort is made to remove in toto the chain, which is then photographed. In this way it is possible to correlate the occasional postoperative findings of areas of excessive sweating with the presence or absence of ganglia in the specimen. The operative mortality rate has been extremely low, only one postoperative death having occurred in 250 patients with essential hypertension.

LORD.

Slocum, H. C., Hoeflich, E. A., and Allen, C. R.: Circulatory and Respiratory Distress From Extreme Positions on the Operating Table. Surg., Gynec. & Obst. **84**:1051 (June), 1947.

The authors have discussed the relation of position on the operating table to the physiology of respiration and circulation. The four factors which normally aid the venous return in raising the blood against gravity are: (1) the impetus given the blood by the contraction of the left ventricle, (2) the support of vein walls due to tonus of the abdominal and limb muscles, (3) the suction and force-pump action on the great veins produced by normal respiratory movements, and (4) the control of the caliber of the venocapillary vessels of the splanchnic area by vasopressor and capillary tonus mechanisms.

They point out how various positions commonly used in surgery influence unfavorably the above factors and also exert a deleterious effect on respiratory movements, both costal and diaphragmatic. The "jack-knife" position for hemorrhoidectomy, the steep Trendelenburg position for pelvic procedures, the elevated kidney and gall bladder rests, and the lithotomy position all produce unfavorable factors for good respiratory and circulatory balance. They show illustrative anesthetic charts to confirm the theoretical considerations. The authors suggest that the flat supine position is the best and that when other positions are necessary they be employed in moderate rather than extreme degrees.

LORD.

Turchetti, A., and Schirosa G.: La Registrazione Grafica della Pressione Venosa. Cuore e circolaz **30**:109, 1946.

By means of a graphic method which permits continuous recording of venous pressure, the slow changes of the latter were investigated. These consist of: (a) respiratory variations, (b) variations due to changes of cardiovascular dynamics, and (c) variations caused by changes of the venous tonus.

A detailed study of the respiratory variations both in the small and large veins of either the superior or the inferior cava district permitted the observation of many interesting data which should be read in the original article.

The graphic record of the cardiovascular variations permitted their analysis and the study of their time relation with both the carotid and the jugular pulsations. The variations of pressure of the right auricle are transmitted to the peripheral veins; however, the waves are gradually damped and reveal various changes of amplitude and shape which are largely the result of the tension existing in the venous system.

The variations of venous tonus are slow (the oscillations last thirty to sixty seconds) and usually irregular; however, they may present periodic oscillations. They may differ in various veins or extend to the whole venous district. Simultaneous variations of the entire venous system were not observed.

LUISADA.

Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients With Chronic Pulmonary Disease and Various Types of Cardio Circulatory Disease. J. Clin. Investigation **25**:639 (July), 1946.

Mean right auricular pressure in resting, recumbent normal subjects varied between + and −2 millimeters of mercury. The pressure variations within the cardiac cycle ranged between 4 and 8 mm. Hg and corresponded closely to Wigger's description of intra-auricular events in the cardiac cycle. During quiet respiration, fluctuations in auricular pressure, while small, were detectable. Maximum right ventricular systolic pressure ranged between 18 and 30 mm. Hg, and averaged 25 millimeters of mercury. Right ventricular pulse pressure varied between 20.5 and 26.5 mm. Hg and averaged 22.5 millimeters of mercury. Right ventricular diastolic pressure was, at times, subatmospheric. The most representative right ventricular pressure curve contour consisted of a rapid systolic rise preceded frequently by a small wave representing auricular systole. At the peak of ventricular systole one or more low frequency oscillations appeared, and following closure of the pulmonic valve, there was usually a small, brief dip below the general level.

Among patients with lesions predisposing to pulmonary hypertension and right ventricular strain and in whom there was no evidence of right heart failure, there were none with elevated ventricular diastolic or auricular pressures. Five patients with therapeutic pneumothorax, two with fibrothorax, two post pneumonectomy, and five of nineteen with pulmonary fibrosis and emphysema exhibited pressures within normal limits. One with kyphoscoliosis, one with mitral stenosis and insufficiency, and fourteen of the group with pulmonary fibrosis and emphysema exhibited elevated ventricular systolic and pulse pressures.

When right heart failure was present ventricular diastolic and auricular pressures were abnormally high and the pressure pulse contours from the right heart and peripheral venous system exhibited characteristic peculiarities except when modified by tricuspid insufficiency. Neither the tracings typical of tricuspid insufficiency nor those characteristic of right heart failure permitted an etiological diagnosis.

A patient with the classical clinical picture of constrictive pericarditis displayed a normal ventricular systolic pressure, high mean auricular and ventricular diastolic pressures, and a low ventricular pulse pressure.

The right heart pressures of several patients with systemic arterial hypertension were within the confines of normal.

Controlled phlebotomy was accompanied by a significant reduction in right ventricular pressures, which returned rapidly to normal following infusion of gelatin solution.

FRIEDLAND.

Cook, C. D., Smith, H. L., Giesen, C. W., and Berdez, G. L.: Xanthoma Tuberosum, Aortic Stenosis, Coronary Sclerosis and Angina Pectoris. Am. J. Dis. Child. 73:327 (March), 1947.

Thannhauser's classification divides primary xanthomatosis into two subgroups: the hypercholesterolemic, and the normocholesterolemic type. In the hypercholesterolemic type xanthoma of the tendons and tendon sheaths, xanthoma tuberosum, and xanthoma planum of the skin, xanthomatosis of the bile ducts with secondary jaundice and biliary cirrhosis, cardiovascular involvement, and scattered nests of xanthoma cells in the spleen, liver, and lymph nodes occur. In the normocholesterolemic type xanthoma disseminatum of the skin, mouth, and larynx, osseous involvement of the skull, scapula, pelvis, extremities, and orbits, xanthomatous involvement of the pituitary gland and tubercle of Rolando with diabetes insipidus, involvement of the brain, medulla, dura, lungs, and pleura, and scattered nests of xanthoma cells in the spleen, liver, and lymph nodes, as in the hypercholesterolemic type, occur. The case presented in this paper is typical of the hypercholesterolemic type because of the cardiac features and xanthoma tuberosum of the skin and xanthoma of the tendons.

The cause of primary xanthomatosis is not known, but Thannhauser has suggested that it is a disease of reticular cells caused by intracellular disorder of cholesterol metabolism. A review of twenty such cases taken from the literature revealed that all were 31 years of age, or less, and that all had definite or probable heart disease. Coronary disease and angina pectoris are common among patients with xanthoma tuberosum, and in the three autopsy cases that have been reported, all were found to have xanthomatous infiltration of the coronary arteries, aorta, and large arteries.

The patient herein described was a 13-year-old boy who had begun to develop soft, fluctuant, yellowish-pink, circumscribed tumors on the elbows, knees, ankles, joints of the fingers and toes, and buttocks. For six to eight months before admission the patient had had dyspnea and substernal pain on exertion. A systolic murmur with its maximal intensity over the aortic area was heard. This murmur was transmitted to the large vessels of the neck and was heard in the back as well. It was thought that the aortic systolic murmur was due to aortic stenosis and that the aortic stenosis was caused by xanthomatous infiltration of the aorta and aortic valves. The blood cholesterol was 561 mg. per 100 c.c.; cholesterol esters, 360 mg.; total fatty acids, 948 mg.; and total lipids, 1,509 milligrams. The level of blood lecithin was 496 mg. per cent. An electrocardiogram taken at rest showed a rate of 86 per minute with isoelectric T waves in Lead II and inverted T waves in Leads III, IVR, and IVF. During an attack of severe substernal pain the rate was 129, and there was considerable depression of the S-T segments in Leads I and II and even more depression in Leads IVR and IVF. The patient was eventually discharged from the hospital and one year later died rather suddenly. Autopsy examination was permitted and the findings confirmed the previous clinical impression. Grade 3 coronary sclerosis with pronounced narrowing of the anterior descending branch of the coronary artery was found, along with a beginning anemic infarct of the lower half of the anterior wall of the left ventricle. The cusps of the aortic valve were thickened and fibrous, and there was some hypertrophy and dilatation present. Microscopically, there were large deposits of fatty material in the myocardium and also in the intima of the coronary arteries.

HAUB.

Downing, M. E.: Blood Pressure of Normal Girls from Three to Sixteen Years of Age. Am. J. Dis. Child. 73:293 (March), 1947.

This article includes a review of the literature and a discussion of various factors that influence blood pressure in young persons, such as age, height, weight, posture, and the width of the cuff used. The purpose of this study was to find the normal blood pressures, using both the child and the adult cuffs, for the same girls who were followed from early childhood into adolescence,

and to find the age or size at which it is best to change from the child to the adult cuff. Weight did not seem very important.

The data presented indicates that height best indicates when to change from the child cuff to the adult cuff. This height is probably in the range of 50.00 to 53.99 inches. The pressure in any one child varies considerably from day to day and even from year to year. In some children there was even a decrease from one year to the next. The most important thing is to know the normal range of blood pressure with the cuff used for the given age and size of child in question, and to know when the child varies from his own normal or from the normal range for his size. If the cuff used for the child is about the same width, in proportion to the size of his arm, as the adult cuff is to the size of the average adult arm the readings are probably comparable.

HAUB.

Wedding, E. S.: Actinomycotic Endocarditis. Arch. Int. Med. **79**:203 (Feb.), 1947.

The literature on bacterial endocarditis due to higher forms of bacteria is reviewed and discloses four cases in which there was a clinical picture without evidence of a portal of entry. In one of the cases reported, inoculation of a rat by a special technique produced pathologic evidence of infection with *Actinomyces*, and the organism was recovered in pure culture from the inoculated animal. Coccal structures, rods, filaments, and branching filaments were observed in vegetations of the aortic valve in the other case, in which an aerobic strain of *Actinomyces* was recovered from the valves, but, in the opinion of the author, contaminants were present in the original culture.

Careful laboratory procedures are the only way in which this diagnosis can be made and differentiated from subacute bacterial endocartitis due to *Streptococcus viridans*.

HORWITZ.

Harris, T. N.: The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever. Am. J. M. Sc. **213**:482 (April), 1947.

The author has confirmed recently reported observations that salicylates may lower the erythrocyte sedimentation rate of nonrheumatic as well as of rheumatic patients. Hence the erythrocyte sedimentation rate may not be relied upon as a criterion of improvement in inflammatory reaction in rheumatic fever. The hypothesis that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient was tested by treating in this way patients in whom the rheumatic process was so active as to produce a prolonged leucocytosis. It was found that, although the erythrocyte sedimentation rate is lowered to normal limits by such treatment, the leucocytosis may remain, although the latter is a much less sensitive indicator of inflammation. This finding is supported by a continued shift to the left in the differential blood count, and by specific signs of continued rheumatic activity which were observed while the erythrocyte sedimentation rate was within normal limits as a result of salicylate treatment. It is doubtful, therefore, that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient or that the lowering of the erythrocyte sedimentation rate in rheumatic patients so treated has the significance attributed to it by Coburn.

DURANT.

Book Reviews

CARDIOVASCULAR DISEASES. David Scherf, M.D., and Linn J. Boyd, M.D., J. B. Lippincott Company, 1947, Philadelphia. With 478 pages, 31 chapters, and 56 illustrations.

The authors state in the preface to this edition of their book that they decided to rewrite it completely and that "In place of a series of essays on selected cardiac problems, a more detailed discussion of cardiovascular diseases is presented in this new volume."

Certain subjects, incompletely considered in previous editions, have been more fully covered, such as rheumatic fever, irradiation of autonomic reflexes, and arteriovenous anastomoses; and the material on others, including roentgenology, myocarditis, and newer therapies, has been expanded.

The book, however, still retains the structure of a series of lectures without any obvious system. The first chapter, for example, is on dyspnea, and the sixteenth chapter is on anginal pain and its differential diagnosis, directly after a chapter on congenital cardiovascular defects. Constant reliance, therefore, on the extensive index is necessary to collect all the information on a single subject. References to the literature, much of it in German, are placed at the end of each chapter and add considerably to the value of the book.

The physiologic discussions, as in the chapters on dyspnea, and compensation and decompensation, are good expositions and cover modern literature satisfactorily. The cardiac manifestations of endocrine disease, especially those in ovarian dysfunction, may not be considered by others to be as specific as they seem to be to these authors, who believe, for example, that sighing respiration on the basis of ovarian hypofunction is "a common and regular finding." It is also stated that "about 22 per cent of all women coming to a cardiologist for advice have complaints referable to disturbance of activity of the ovaries."

In the consideration of mitral stenosis the authors state that the presystolic murmur is the first one to appear in the usual development of this lesion, and relate it to the increased velocity of the blood with auricular contraction. It is the experience of the reviewer that the mid-diastolic murmur occurring during the rapid inflow stage of ventricular filling is more often the herald of beginning stenosis, even though it may be, for a time, indistinguishable from the murmur of left ventricular dilatation in active rheumatic carditis. One notes, also, no discussion of hemoptysis as a complication of mitral stenosis.

The relatively little attention given to electrocardiography is intentional, as this lack has been supplied by the authors in their companion volume on Clinical Electrocardiography.

Recommendations for therapy conform in general to the accepted procedures. It may be noted, however, that the use of leeches over the liver in acute congestion and over the veins in painful thrombophlebitis is still defended. It is wisely pointed out that the bradycardia of aortic stenosis and of complete heart block should not preclude digitalis therapy when otherwise indicated. As one of the causes of the small left ventricle in mitral stenosis, the limitation of physical effort by dyspnea is cited, and it is recommended that patients should be encouraged to continue exercise which does not produce symptoms to prevent this atrophy of the heart.

Aminophylline suppositories are advised as the "safest and most gratifying" therapy for heart block with Adams-Stokes attacks, but the authors warn against theobromine, caffeine, and theophylline in patients in whom the danger of thrombosis exists, due to their effect in causing hyperthrombinemia. Combining ephedrine and barium chloride in heart block is considered dangerous, as it will often evoke ventricular fibrillation.

The authors' interest in myocarditis re-emphasizes a subject worthy of consideration, especially in view of recent evidence of virus injury to heart muscle, as in primary atypical pneu-

monia and mumps. They repeat the assertion of earlier editions that "only a few individuals completely and permanently escape small inflammatory foci in the myocardium (myocarditis)."

There is a full consideration of coronary artery disease in the chapter on anginal pain. It is emphasized that in the examination of elderly individuals prior to operation "it is safer to state that the examination does not disclose coronary sclerosis than to say that coronary sclerosis is absent."

With myocardial infarction, "pericarditis, in general, represents a desirable complication, for the local inflammation speeds the healing process."

The occurrence of a deep Q wave in Lead I in the electrocardiogram of patients who once had a myocardial infarction supports a suspicion of cardiac aneurysm.

Dupuytren's contracture, as well as the more common painful shoulder, may follow myocardial infarction.

Peripheral vascular disease is covered in a forty-four page section, and the final chapter of thirty-nine pages is concerned with therapy.

The knowledge of cardiovascular disease is brought well up to date in this volume. The few omissions are dependent upon the present velocity of the stream of information concerning circulatory disorders. The great value of venous catheterization of the heart in the diagnosis of congenital heart disease is not mentioned. Ligation and division, which has in the main replaced simple ligation of the patent ductus, is also omitted, as is the very recent operation of anastomosis of aorta and pulmonary artery in certain congenital cardiovascular defects associated with cyanosis. The newer concepts concerned with fluid retention and sodium excretion mechanisms in congestive failure are not emphasized to the degree that seems at present justified.

It is recommended that this book be read in its entirety to obtain a useful review of cardiovascular physiology, diagnosis, and treatment. It does not cover the field of electrocardiography, but with a total of 1,984 references to literature on the circulation, it can well serve as a bibliography of the general field of diseases of the heart and blood vessels.

HOWARD B. SPRAGUE.

LE FORME CLINICHE ATIPICHE DELL'INFARTO MIOCARDICO. By Iandolo, C., Edizioni Scientifiche Italiane, Naples, Italy, 1946, with 102 pages.

This monograph deals with cases of myocardial infarction which have an atypical clinical picture. Following a scheme which reminds one of the traditions of the French school, the author describes: (1) Infarctions with few clinical signs (so-called mild cases). (2) Infarctions where one clinical sign (pain, fever, collapse, or dyspnea) is predominant. (3) Infarctions with an atypical picture in which various abdominal, respiratory, or metabolic syndromes may be simulated. The study of Iandolo is based on personal observation of twenty-two atypical cases out of a series of 165 cases of infarction (13.3 per cent). The discussion is supplemented by brief reports of all the atypical cases.

While the book does not add to what is already known, it may emphasize the need for a more detailed consideration of the atypical and mild types of myocardial infarction.

A. LUISADA.

DIAGNOSTIC ELECTROCARDIOGRAPHIQUE. By André Jouve, Jaques Senez, and Jean Pierron, Masson & Cie, Paris, 1946, with 336 pages and 217 illustrations.

This volume, it appears, represents the first textbook on electrocardiography in France, and therefore is destined to assume an authoritative position in the European literature. The text is sound and conservative and is conventionally divided into four sections. A discussion of basic theories and techniques is followed by a section dealing with the normal variations of the electrocardiographic curve, which includes a chapter on the theoretical interpretation of such records. The third part comprises a section on the abnormal electrocardiogram and cardiac arrhythmias. The fourth section attempts to correlate electrocardiographic patterns with certain diseases, drug actions, and clinical syndromes.

The reviewer finds that the wealth of factual material presented often overshadows the basic principles necessary for understanding and interpretation of an electrocardiogram. The

spread of the action current over auricular and ventricular muscle, as traced and analyzed by many workers, has a direct bearing on the form and shape of any electrocardiographic lead. Familiarity with the laws which govern the distribution of currents in conductors such as the heart is of far more direct benefit to the student than the memorizing of certain patterns. Yet, in texts of this sort, such basic information is usually treated in small print as a necessary evil rather than as a foundation upon which to base the teaching of clinical electrocardiography. Similarly, the use of precordial or esophageal leads is treated as an additional new subject rather than as an integral part bridging the way from experimental curves obtained from endocardial and epicardial surfaces to unipolar and bipolar limb leads. The lack of such integration results in the accumulation of empirical facts rather than in a logical explanation of the abnormal electrocardiogram in myocardial infarction, bundle branch block, extrasystoles, and similar abnormalities. On the other hand, too much emphasis is perhaps placed on the calculation of the direction of the electrical axes which are of limited value in clinical electrocardiography. The extension of Einthoven's theorems to include important concepts, such as the calculation of the area of electrocardiographic deflections and the ventricular gradient, receive scant attention indeed.

The difficulties under which this book must have been written explains perhaps some of its defects, although much of this information was known to, and published by, European investigators before the war. This probably accounts also for the peculiar nomenclature and adherence to the earlier methods of recording precordial leads in which a positivity of the exploring electrode was represented by a downward deflection. This will undoubtedly revive some of the earlier confusion. The new method reversing the original polarity was common usage in Germany, Switzerland, and the Scandinavian countries before its universal acceptance in the United States, Great Britain, and South America.

The fundamental criticism which must be stressed is one that may be made for all but a few texts on the subject. This book compares very favorably with others in presenting the results of experimental and empirical information. The attempt to correlate clinical syndromes with electrocardiographic patterns, to which one-fourth of the book is devoted, is an extremely difficult one and is handled sparingly and with great reservation. One would wish that in future editions this section would be expanded and perhaps more profusely illustrated. It is one to which the beginner as well as the clinician familar with the subject matter will turn to most readily. In its present form this section will leave many questions unanswered.

As it stands, the book has great merits and will undoubtedly receive the credit it really deserves. It is beautifully written, easily understood, and impeccably set to type. The illustrations, which are often accompanied by sound records, are well selected and in the main are excellently reproduced.

H. H. HECHT.

LA DIGITALE ET LES STROPHANTINES. PHARMACODYNAMIE—THERAPEUTIQUE. By D. Danielopolu, Bucharest. Masson & Cie Editeurs, Paris, 1946. With 206 pages and 56 illustrations.

Danielopolu, who occupied himself with the physiology and pharmacology of the vegetative nervous system for thirty years, in his new book on digitalis and strophanthines presents his views on the action of digitalis and allied drugs. These views are based on his experimental studies and clinical observations, and stem from his personal interpretation of the vegetative system.

Digitalis has no effect on the heart nerves and, in therapeutic doses, exerts no influence on the myocardium. Its action is achieved by its effect on both acetylcholine and sympathin: by inhibiting the cholinesterase (antiacetylcholinolytic effect) it protects acetylcholine from being hydrolysed; simultaneously, it intensifies the effectiveness of sympathin. Since mediators of both systems are always influenced, digitalis is called "amphotropic with predominant effect on one or the other component."

Digitalis in large doses has a "specific" (toxic) effect on the heart muscle; the cell plasma is damaged irreversibly. In therapeutic doses, the "nonspecific" effect is brought about: the drug produces augmentation of irritability, contractility, and tonicity through enhancing the action

of sympathin on the adult type of fibers; whereas the inhibiting effect of the same dose on rhythmicity and conductivity is attributed to its acetylcholinergic action on the embryonic type of fibers.

In addition to the usual indications, digitalis is recommended for the treatment of essential hypertension ("the best hypotensive drug we possess") and angina pectoris. The acetylcholine spared from lysis will produce a hypotensive effect by its action on small vessels. Anginal attacks are prevented by the lowered blood pressure, by the augmented myocardial blood flow of a lengthened diastole, and by an increase of myocardial resistance against fatigue.

Danielopolu is an ardent advocate of strophanthin. He uses it in intramuscular injections and considers it the drug of choice in acute myocardial insufficiency of infectious origin and in chronic heart failure complicated by a febrile disease. Strophanthin is occasionally effective when digitalis fails.

The book also contains a chapter on the history of the use of digitalis, as well as one giving a very exhaustive presentation of the author's theory of the function of the vegetative system.

The section dealing with digitalis and the electrocardiogram appears simply at odds with facts.

An outstanding feature of the book is its lively style. Although the points of view on the action of digitalis, as exposed, differ from those accepted in this country, it cannot be denied that they have been brought into a unified system harmonizing with the author's conception of vegetative physiology.

The absence of a table of contents and of an alphabetical index makes the orientation in the text rather difficult. The print is poor and typographical errors abound.

J. BRUMLIK.

American Heart Association, Inc.

1790 Broadway, New York 19, N. Y.

Telephone Circle 5-8000

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.

The Chairman of the Program Committee for the Annual Scientic Session is Dr. Herrman L. Blumgart, 330 Brookline Avenue, Boston, Massachusetts. All who desire to present papers at the meetings in Chicago on June 18 and 19 should forward to Dr. Blumgart an abstract of the proposed presentation of not more than 500 words. The dead line for the receipt of abstracts is Feb. 1, 1948.

MEMBERSHIP

The American Heart Association and its local affiliates throughout the United States have agreed upon a system of interrelated membership. New members residing in areas where local Heart Associations exist shall be joint members of both the local and the American Heart Association. New members resident in areas where no local affiliated Heart Association exists may apply directly for membership. In addition to physicians, members of other professional groups and laymen are now welcome as members of the American Heart Association.

Membership blanks will be sent upon request, as well as information about membership in local Heart Associations. The following types of membership are provided by the American Heart Association.

Annual Membership.....$ 2.50	Contributing Membership.....$25.00
Journal Membership.....$10.00	Patron Membership.....$50.00 or more

The dues of the local Heart Associations are added to these.

Annual Membership includes twelve issues of *Modern Concepts of Cardiovascular Disease*

Journal Membership includes a year's subscription to the American Heart Journal (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease* and annual membership in the Association. (A special Journal Membership for the remainder of 1947 is available for a limited time. Details will be given on request.)

Subscription to the American Heart Journal through the publishers does not provide for membership in the American Heart Association, except as provided for in a Journal Membership.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

OFFICERS

President
DR. ARLIE R. BARNES

President Elect
DR. TINSLEY R. HARRISON

Vice-President
DR. CARL J. WIGGERS

Treasurer
SAMUEL HARRELL

Secretary
DR. HARRY E. UNGERLEIDER

Executive Secretary
DR. H. M. MARVIN

Medical Director
DR. CHARLES A. R. CONNOR

BOARD OF DIRECTORS

*THOMAS I. PARKINSON, Chairman.....New York City
DR. EDGAR V. ALLEN.....Rochester, Minn.
*DR. E. COWLES ANDRUS.....Baltimore
*DR. ARLIE R. BARNES.....Rochester, Minn.
DR. WILLIAM H. BUNN.....Youngstown, Ohio
*DR. GEORGE E. BURCH.....New Orleans
*S. DEWITT CLOUGH.....Chicago
*COLGATE W. DARDEN, JR.....Charlottesville, Va.
*JUSTIN DART.....Los Angeles
DR. CLARENCE E. DE LA CHAPELLE.....New York City
DR. GEORGE K. FENN.....Chicago
DR. MORRIS FISHBEIN.....Chicago
RUDOLPH F. HAFFENREFFER.....Providence
*SAMUEL HARRELL.....Indianapolis
*DR. TINSLEY R. HARRISON.....Dallas
ALFRED C. HOWELL.....Bethel, Conn.
*DR. T. DUCKETT JONES.....Boston
DR. LOUIS N. KATZ.....Chicago
DR. JOHN D. KEITH.....Toronto, Can.
DR. ROBERT L. KING.....Seattle
MRS. WENDELL KINNEY.....Los Angeles
DR. WILLIAM B. KOUNTZ.....St. Louis
DR. EUGENE M. LANDIS.....Boston
DR. ROBERT L. LEVY.....New York City
DR. H. M. MARVIN.....New Haven, Conn.
DR. THOMAS M. MCMILLAN.....Philadelphia
*ROBERT L. MEHORNAY.....Kansas City, Mo.
*DR. IRVINE H. PAGE.....Cleveland
*DR. JOHN J. SAMPSON.....San Francisco
DR. HOWARD B. SPRAGUE.....Boston
DR. EUGENE A. STEAD, JR.....Durham, N. C.
DR. J. ROSS VEAL.....Washington, D. C.
DR. HARRY E. UNGERLEIDER.....New York City
DR. HOWARD F. WEST.....Los Angeles
DR. CARL J. WIGGERS.....Cleveland
*DR. IRVING S. WRIGHT.....New York City

*Executive Committee.

ASSEMBLY

DR. EDGAR V. ALLEN.....Rochester, Minn.
JAMES ANDERSON.....Philadelphia
DR. E. COWLES ANDRUS.....Baltimore
DR. GRAHAM ASHER.....Kansas City, Mo.
DR. ARLIE R. BARNES.....Rochester, Minn.
DR. EMMET B. BAY.....Chicago
DR. ALFRED BLALOCK.....Baltimore
ALVA BRADLEY.....Cleveland
EARLE BROWN.....Minneapolis
DR. LEWIS T. BULLOCK.....Los Angeles
DR. WILLIAM H. BUNN.....Youngstown, Ohio
DR. GEORGE E. BURCH.....New Orleans
DR. EDWARD W. CANNADY.....East St. Louis, Ill.
HARRY C. CARR.....Philadelphia
DR. FRANCIS L. CHAMBERLAIN.....San Francisco
PAUL F. CLARK.....Boston
S. DEWITT CLOUGH.....Chicago
DR. WARREN B. COOKSEY.....Detroit
CHANNING H. COX.....Boston
JAMES A. CUNNINGHAM.....Chicago
COLGATE W. DARDEN, JR.....Charlottesville, Va.
JUSTIN DART.....Los Angeles
DR. CLARENCE E. DE LA CHAPELLE.....New York City
DR. GEZA DE TAKATS.....Chicago
DR. FRANCIS R. DIEUAIDE.....New York City
DR. HARVEY M. EWING.....Montclair, N. J.
DR. GEORGE K. FENN.....Chicago
RICHARD J. FINNEGAN.....Chicago
DR. MORRIS FISHBEIN.....Chicago
DR. NORMAN E. FREEMAN.....San Francisco
ARTEMUS L. GATES.....New York City
SAMUEL GOLDWYN.....Los Angeles
A. E. GRAUER.....Vancouver, B. C., Can.
DR. JAMES A. GREENE.....Houston
RUDOLPH F. HAFFENREFFER.....Providence
SAMUEL HARRELL.....Indianapolis
RICHARD F. HARRISON.....Syracuse, N. Y.
DR. TINSLEY R. HARRISON.....Dallas
DR. JOHN HEPBURN.....Toronto, Can.
DR. GEORGE R. HERRMANN.....Galveston
DR. J. G. FRED HISS.....Syracuse, N. Y.
ALFRED C. HOWELL.....Bethel, Conn.
DR. W. C. HUEPER.....New York City
COLEMAN JENNINGS.....Washington, D. C.
DR. T. DUCKETT JONES.....Boston
DR. ALBERT D. KAISER.....Rochester, N. Y.
DR. LOUIS N. KATZ.....Chicago
SAMUEL H. KAUFFMANN.....Washington, D. C.
DR. JEROME G. KAUFMAN.....Newark, N. J.
DR. JOHN D. KEITH.....Toronto, Can.
DR. ROBERT L. KING.....Seattle
MRS WENDELL KINNEY.....Los Angeles
DR. WILLIAM B. KOUNTZ.....St. Louis
DR. CHESTER M. KURTZ.....Madison, Wis.
DR. EUGENE M. LANDIS.....Boston
DR. BERNARD W. LEONARD.....Washington, D. C.
DR. ROBERT L. LEVY.....New York City
CLARE BOOTHE LUCE.....Ridgefield, Conn.
DR. HAROLD C. LUETH.....Omaha
RUTH E. LYNCH.....Los Angeles
DR. LOUIS E. MARTIN.....Los Angeles
DR. H. M. MARVIN.....New Haven, Conn.
DR. EDWIN P. MAYNARD, JR.....Brooklyn
DR. SAMUEL J. MCCLENDON.....San Diego
ALFRED J. MCCOSKER.....New York City
DR. HUGH MCCULLOCK.....St. Louis
DR. JOHNSON MCGUIRE.....Cincinnati
DR. THOMAS M. MCMILLAN.....Philadelphia
ROBERT L. MEHORNAY.....Kansas City, Mo.
DR. J. ROSCOE MILLER.....Chicago
RICHARD M. MOSS.....Belleville, Ill.
DR. E. STERLING NICHOL.....Miami
DR. FRANKLIN R. NUZUM.....Santa Barbara, Calif.
DR. IRVINE H. PAGE.....Cleveland
THOMAS I. PARKINSON.....New York City
DR. MYRON PRINZMETAL.....Los Angeles
DR. SAMUEL PROGER.....Boston
DR. DICKINSON W. RICHARDS, JR.....New York City
DR. HAROLD H. ROSENBLUM.....San Francisco
DR. PHILIP ROSENBLUM.....Chicago
DR. HOMER P. RUSH.....Portland, Ore.
DR. JOHN J. SAMPSON.....San Francisco
DR. FRANCIS T. SCHWENTKER.....Baltimore
DR. HAROLD N. SEGALL.....Montreal, Can.
DR. ARTHUR SELZER.....San Francisco
DR. M. J. SHAPIRO.....Minneapolis
DR. HOWARD B. SPRAGUE.....Boston
DR. ISAAC STARR.....Philadelphia
HAROLD E. STASSEN.....St. Paul
DR. EUGENE A. STEAD, JR.....Durham, N. C.
DR. ERNEST L. STEBBINS.....Baltimore
DR. WILLIAM D. STROUD.....Philadelphia
DR. HOMER F. SWIFT.....New York City
DR. ALEXANDER W. TERRELL.....Dallas
DR. WILLIAM P. THOMPSON.....Los Angeles
DR. HARRY E. UNGERLEIDER.....New York City
DR. J. ROSS VEAL.....Washington, D. C.
DR. LOUIS E. VIKO.....Salt Lake City
DR. MAURICE VISSCHER.....Minneapolis
JOE E. WERTHAN.....Nashville
DR. HOWARD F. WEST.....Los Angeles
DR. PAUL D. WHITE.....Boston
CARL WHITMORE.....New York City
DR. CARL J. WIGGERS.....Cleveland
DR. FRANK N. WILSON.....Ann Arbor
DR. J. EDWIN WOOD, JR.....Charlottesville, Va.
GUS S. WORTHAM.....Houston
DR. IRVING S. WRIGHT.....New York City
J. D. ZELLERBACH.....San Francisco